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The Role of Chemistry in Preventing Obesity

American society is today faced with an obesity crisis. It is ironic that a country so consumed with self-image is also one where 130 million adults are overweight or obese. Because obesity causes serious health problems, it presents a worldwide threat. The increasing population of obese persons can be attributed to inappropriate food choices, a sedentary lifestyle, and lack of exercise. The health and economic concerns of obesity call for scientists to investigate the causes of the growing epidemic. Chemical scientists are analyzing the chemistry of food, trying to determine the factors that promote obesity at the cellular level. Chemical innovations such as artificial sweeteners and fat replacers can help to reduce the adverse health effects of excessive consumption of sugar and fat.

Factors Leading to Obesity

Overweight and obese are labels attributed to persons who weigh more than the healthy weight corresponding to their height. For adults, the ranges for overweight and obese are specified using the Body Mass Index (BMI) that is calculated from an individual’s weight and height. BMI correlates with the amount of body fat. To calculate BMI, adults divide their weight in kilograms by the square of their height in meters ($BMI = kg / m^2$). Adults with a BMI of 25-29.9 are overweight, while those with a BMI of 30 or greater are obese.

There is not one cause of obesity; a variety of factors play a role, including energy imbalance due to consumption of too many calories and insufficient physical activity, genetic predisposition, metabolism, culture, and environment.

Health and Economic Concerns

Obesity has risen dramatically in the United States, with over 65% of adults over age 20 overweight or obese and 15% of children ages 6-19 obese. Obesity threatens the nation's health: obesity is a leading cause of coronary heart disease and heart attack. In many cases, obesity is responsible for raising blood cholesterol levels and blood pressure, for lowering HDL cholesterol (good cholesterol), and for predisposing individuals to diabetes.

Medical costs indicate that obesity is a growing health problem. The Center for Disease Control reports that in 2003, medical expenditures attributed to obesity reached $75 billon, including state-level expenditures of $7.7 billion in California alone. The financial consequences of obesity are severe; taxpayers cover half of the fees through Medicare and Medicaid programs.

Artificial Sweeteners

In an effort to promote healthier food choices, and to combat the increasing consumption of high-calorie and high-fat foods, health professionals have turned to scientists to modify some common food ingredients to make them low-fat or sugar-free. A well-known example is the introduction of artificial sweeteners. About 60% of sugar intake for Americans is attributed to corn sweeteners while the other 40% comes from table sugar. Large quantities of sugar add to the surplus of calories consumed and contribute to weight gain. As a result, the Food and Drug Administration has approved sugar substitutes such as aspartame, saccharin, and sucralose to lower calorie intake and to provide a proper alternative to sugar for diabetics. The American Diabetes Association refers to sugar substitutes as "free foods" because they are nearly calorie-free and do not raise blood-sugar levels. Consumers have responded favorably to "sugar-free" foods. In the U.S., sales of sugar free foods and beverages reached 5.9 billion dollars in 2005 and are set to reach 7.7 billion in 2010.

Measuring Sweetness

We do not have any laboratory instruments for measuring the sweetness of a substance, and there are no units of sweetness. Thus, when scientists discuss sweetness for a particular substance, they refer to the sweetness measured by the human tongue and to data accumulated from numerous comparisons of sweetness values. Sweetness refers to the ability of a molecule to interact with certain taste receptors in the mouth and is usually measured by performing serial dilutions of the substance; a panel of people taste and record at which concentration sweetness is no longer tasted. Sweetness values are expressed relative to an arbitrary standard, usually sucrose, (table sugar), whose sweetness value is 1.

Saccharin

Saccharin (generic name for benzoic sulfinide) is the oldest sugar substitute. It was discovered in 1878 by Constantin Fahlberg and Ira Remsen of John Hopkins University. While attempting to oxidize toluene sulfonamides, Fahlberg discovered that one of his products tasted very sweet. Fahlberg named it saccharin from the chemical name for sucrose: saccharose. Today, chemists synthesize saccharin from toluene or by reacting anthranilic acid with nitrous acid, sulfur dioxide, chlorine, and then ammonia. Saccharin is a heterocyclic compound shown in Figure 1; it has a sweetness value of 300 relative to sucrose but it can have a bitter aftertaste at high concentrations. [1] Saccharin is a stable compound upon heating and does not react with other food ingredients.

Saccharin has been available for consumption since the early 1900's and is today the main ingredient of the artificial sweetener Sweet'N Low, available in pink packets. Products that contain saccharin often also contain sodium or calcium salts that are highly soluble and promote quick dissolution in liquids. A packet of Sweet'N Low contains 36 mg of calcium saccharin in addition to small amounts of dextrose (a filler), cream of tartar (a taste modifier), and calcium silicate (an anti-caking agent).

Saccharin has been a source of controversy. In the 1960s, toxicity experiments classified saccharin as a potential animal carcinogen. When lab rats were fed large doses of saccharin they developed bladder cancer. Following a thorough investigation, the U.S. Congress required all packages of saccharin to contain a warning label indicating its potential as a carcinogen. However, the study that deemed saccharin a carcinogen was misleading because the lab rats were fed saccharin in huge quantities; impurities in the sugar, not saccharin itself, seemed to cause the cancers. In 2000, Congress revoked the law requiring that health hazards be indicated on packages containing saccharin.

Aspartame

Aspartame is another widely-used artificial sweetener, a methyl ester derived from the dipeptide bond of the amino acids aspartic acid and phenylalanine.[2] In 1965, James Schlatter of G.D. Searle & Co. was synthesizing peptide drugs when he found a sweet-tasting substance on his fingers. The compound, shown in Figure 2, was given the name “aspartame,” a simplification of aspartylphenylalanine methyl ester. Today, chemically synthesized aspartame is the primary ingredient of the artificial sweetener *Equal*. Aspartame is found in more than 6,000 products including soft drinks, puddings, and frozen desserts. Aspartame is about 200 times sweeter than sucrose. The caloric value of aspartame is about 4 kilocalories per gram but, because very small quantities are sufficient to produce a sweet taste, the caloric intake is insignificant. Aspartame is not as stable as saccharin; it degrades when heated and loses its sweetness. Under strongly acidic or alkaline conditions, aspartame produces methanol by hydrolysis. Methanol is metabolized to formic acid and formaldehyde, classified as a potential human carcinogen by the World Health Organization.

The controversy over aspartame's safety demanded a thorough investigation, culminating in the approval of the sweetener for use in 1981. Methanol is lethal to humans in large quantities but, because aspartame is used in small amounts, it does not reach toxic levels. Under extreme conditions, aspartame dissociates into its component amino acids. Thus aspartame is not suitable for individuals diagnosed with phenylketonuria (PKU). People born with phenylketonuria are not able to metabolize phenylalanine; to avoid brain damage, they must avoid aspartame or monitor their intake of this amino acid.

Sucralose

The artificial-sweetener market is currently dominated by sucralose, known by the brand name Splenda, accounting for 50% of the sugar-substitute market. Sucralose is the only high-intensity synthetic sweetener currently made from sucrose. Sucralose was discovered in 1976 when a scientist at the British sugar company Tate & Lyle set out to create new products from sucrose by testing chlorinated sugars as chemical intermediates. Splenda was approved for use by the FDA in 1998. Splenda packages contain sucralose combined with small amounts of the common food ingredients dextrose, the D-isomer of glucose, and maltodextrins that are used to give the compound volume.

As shown in Figure 3, sucralose is a chlorocarbon made by replacing three hydroxyl groups with three chlorine atoms on the sucrose molecule.[3] Chemists take an eyedropper full of sulfuryl chloride, a highly toxic compound, and add it to a sugar solution one drop at a time. An intense reaction ensues to produce 1', 4, 6, 6'-tetrachloro-1', 4, 6, 6'-tetradeoxygalactosucrose. Organic molecules containing chlorine atoms are often sweet; sucralose is 600 times sweeter than sucrose and is safe for consumption. The enhancement of sweetness of the derivative is due first, to the increased hydrophobicity of the CH_2Cl groups and second, due to specific interactions with water. Although sucralose is made from sugar, the body does not recognize it as a sugar or a carbohydrate. Because sucralose is not metabolized for energy, it is calorie-free. The solubility of sucralose in water increases with temperature and it is stable in a broad pH range in aqueous systems. At a pH of 3 or lower, some hydrolysis occurs; at pH 4-7.5 no sucralose is lost in solution.

Splenda's slogan, "Made from sugar so it tastes like sugar" is a topic of recent debate that has brought chemistry to court. The trial focused on a battle between two sugar-substitute giants, Equal and Splenda, the parties eventually reaching an undisclosed settlement. Merisant, the maker of Equal sued McNeil Nutritionals, the maker of Splenda over misleading advertisements that proclaim Splenda contains sugar and is natural. Merisant believes this claim is false because the sucrose is chemically modified. Splenda's defense is that the product tastes like sugar because it is a derivative of sugar and reacts similarly with sweet-taste receptors in the mouth. Sucralose attaches to two sweet receptors, T1R2 and T1R3 exactly as sugar does and brings about the same cellular changes. The only difference is that sucralose binds more tightly, producing its overwhelming sweet taste. To prove this, the defense used data gathered from fluorescence spectroscopy which compared the binding affinities of sucrose and sucralose. A synchrotron was also used to measure the conformational change of the receptor when the sugar is bound to it. Equal's advocates believe that Splenda's slogan is misleading to consumers and fails to acknowledge that it is an artificial sweetener. Indeed, the fierce advertising campaign of Splenda manufacturers has resulted in over $212 million in annual sales in the U.S., dwarfing Equal's sales of $49 million.

Fat-conscious Consumers

Fats have long been the enemy of individuals striving to lose weight because fats are the body's most concentrated source of energy. Furthermore, fats cause significant health risks. Trans fats[1] have recently come under scrutiny, as studies have shown increased risk for coronary heart disease and diabetes for individuals consuming large amounts of trans fats.[4]

To reduce fat intake, scientists have introduced fat substitutes for use in foods. These fat substitutes promote the consumption of low-fat foods (defined as having no more than 3 grams of fat per 50 grams of food) to remove the risk of increased cholesterol and saturated fat associated with a high-fat diet.

Fat substitutes replace the calorie content provided by fats (9 kcal/g) while maintaining the texture and flavor of foods many of us enjoy. Fat replacers fall into two categories: food additives and "generally recognized as safe" (GRAS) substances. Food additives must be approved by the FDA. Examples of food additives include polydextrose, carrageenan and olestra. GRAS substances do not undergo rigorous testing because they are known for their long history of safe use in other foods. Examples of GRAS substances used as fat replacers are cellulose gel, known for its fat-like properties, dextrins (thickener), and guar gum (improves texture and shelf life).

Carbohydrate-based Fat Replacers

Fat replacers can be carbohydrate, protein or fat-based. Many carbohydrate-based replacers are labeled as GRAS and have been used mainly as thickeners and stabilizers. One of the first fat replacers to become available was carrageenan, which uses carbohydrates as the main ingredient. As shown in Figure 5, carrageenan is a linear sulphated galactose polysaccharide

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[1] Trans fat is the *trans* isomer of an unsaturated fatty acid, consisting of one (monounsaturated) or more (polyunsaturated) double bonds.

prepared by alkaline extraction from red seaweed. The molecule consists of alternating 3-linked-β-D-galactopyranose and 4-linked-α-D-galactopyranose units.[5] Because carrageenan is flexible, it can curl to form helical structures that form a gel. Thus, carrageenan was approved for use as an emulsifier and thickener of food and in the 1990's, it became a popular fat-replacer.

Polydextrose is also a common ingredient because it increases fiber content. Polydextrose is a humectant, which means that it helps retain moisture. Dextrins and maltodextrins (a group of low-molecular-weight carbohydrates produced by hydrolysis of starch), fiber, gums are also used to retain moisture. Dextrins are mixtures of linear α-(1,4)-linked D-glucose polymers and have a shorter chain length than carbohydrates.[6] They are water soluble and easily digested. Carbohydrate-based fat replacers add bulk to food and thicken the food to provide a consistency similar to that of fat. These ingredients help reduce caloric intake and can be used as thickeners in such foods as frozen desserts, baked goods, and sauces.

Protein-based Replacers

An example of a protein-based fat replacer is Microparticulated Protein Product (MPP), made from whey protein or milk and egg protein. MPP is not suitable for heating but is approved in frozen desserts.

Fat-based Replacers

Fat-based replacers are widely used to mimic the properties of fats we crave to eat. One of the most prevalent fat-replacers is Olestra, a sucrose polyester made in 1996 by Procter & Gamble and first used in potato chips. Olestra is derived from soybean, sunflower, or corn fatty acids and has properties similar to those of fats but contains no calories because it is undigestable. Fats consist of a glycerol molecule with three fatty acid tails attached.[7] Shown in Figure 8 is Olestra, a sucrose polyester connected to up to eight fatty acids, which give it an octopus-like structure.[8] Because the fatty acids block access to the sucrose molecule, enzymes cannot break it down and Olestra passes through the digestive system unabsorbed. Synthesis of the molecule as a sugar allows heating to high temperatures, as in frying. However, Olestra has come under some scrutiny, as it may cause abdominal cramps and loose stool. Further, Olestra reduces absorption of fat-soluble vitamins A, D, E and K.

Appetite Suppressants

As more consumers have become concerned with the harmful health effects of obesity and with body image, there has been a growing trend in the consumption of appetite suppressants, also called anorectics. Compounds marketed as anti-obesity preparations include *Fastin*, *Adipex*, and *Tenuate*. *Fastin* and *Adipex* contain phentermine[9], a suppressant from the amphetamine and phenetyhlamine family while *Tenuate* has a mechanism of action similar to that of diethylpropion, a stimulant drug.[10] These active ingredients affect the central nervous system and stimulate neurotransmitters to release catecholamines, which signal a flight-or-fight body response and suppress hunger signals. Many appetite suppressants are similar to amphetamines (phentermine) and antidepressants (diethylpropion). They are classified as controlled substances in the United States because they can lead to dependence if taken for long periods of time. Due to their catecholamine-releasing properties, many appetite suppressants cause increased heart rate and blood pressure, leading to possible heart attack when combined with other drugs.

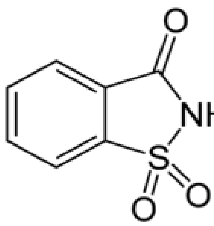
Orlistat: Inhibitor of Fat Absorption

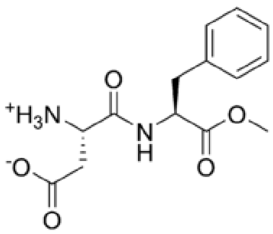
A popular drug used today to treat overweight or obese individuals is orlistat, also known as tetrahydrolipstatin.[11] Orlistat is marketed under the trade name *Xenical* by Roche, and an over- the-counter version, *alli,* produced by GlaxoSmithKline. More than 2 million starter packets of *alli* have been sold since its release in June 2007.

Orlistat prevents absorption of fats from the human diet and thus reduces caloric intake. Shown in Figure 11, Orlistat is a saturated derivative of lipstatin, a natural inhibitor of pancreatic lipases isolated from bacteria. Orlistat inhibits the enzyme pancreatic lipase, which breaks down triglycerides in the intestine. Without this lipase, triglycerides cannot be hydrolyzed into fatty acids; thus, they are excreted undigested. At a standard dosage of Xenical, 120 mg, orlistat prevents 30% of fat from absorption. In addition, findings presented at the 2006 International Congress on Obesity revealed that users of orlistat showed decreases in total cholesterol, LDL cholesterol, and systolic and diastolic blood pressure levels when compared to a placebo.

Conclusion

It is a paradox that even with the variety of healthier food substitutes, the waistlines in America keep growing. Synthetic chemists have made a major contribution by finding substitutes for sugar and for fat and by synthesizing drugs to reduce fat absorption. But chemical science can only go so far to promote nutritional choices. As chemists delve more into the details of hunger and metabolism, and as schools make an effort to promote healthier eating for children and as campaigns to increase exercise become more successful, obesity can hopefully be reduced in the next generation.

1  Figure 1: Saccharin

2  Figure 2: Aspartame

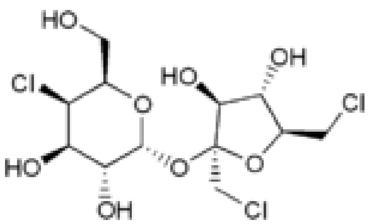
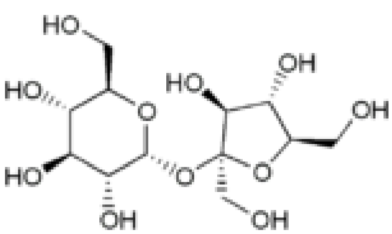
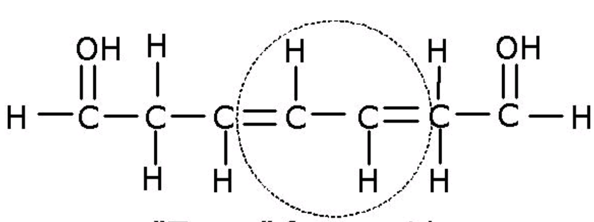


Figure 3: Comparison of the chemical structures of sucralose (top)

and sucrose (bottom).



4 

"Trans" fatty acid

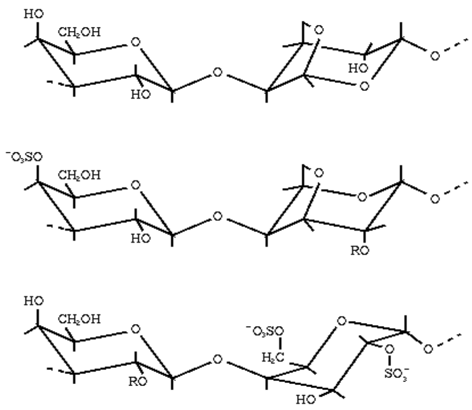


Figure 5: Carrageenan

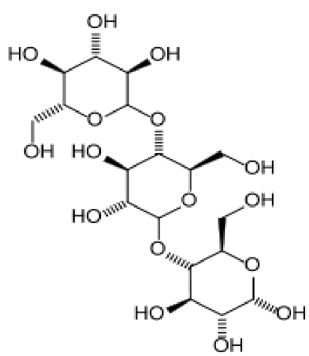
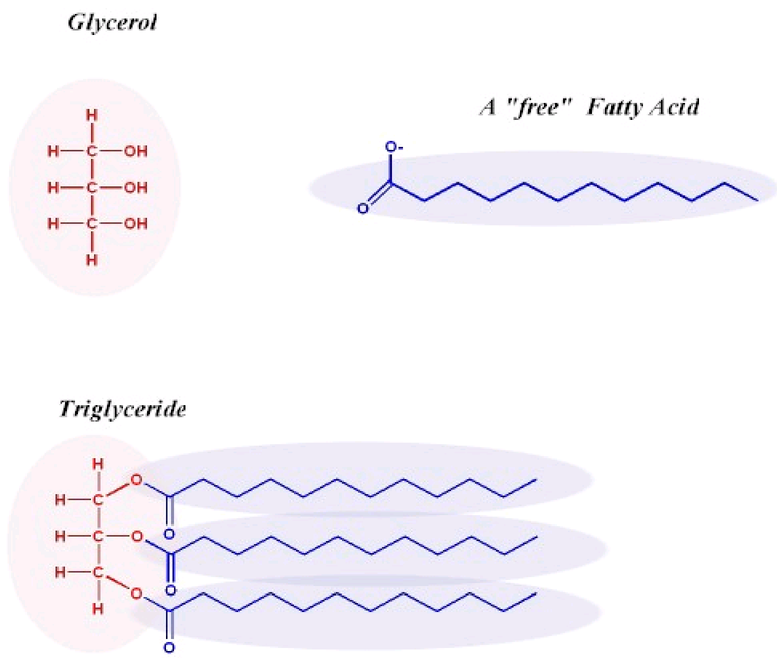
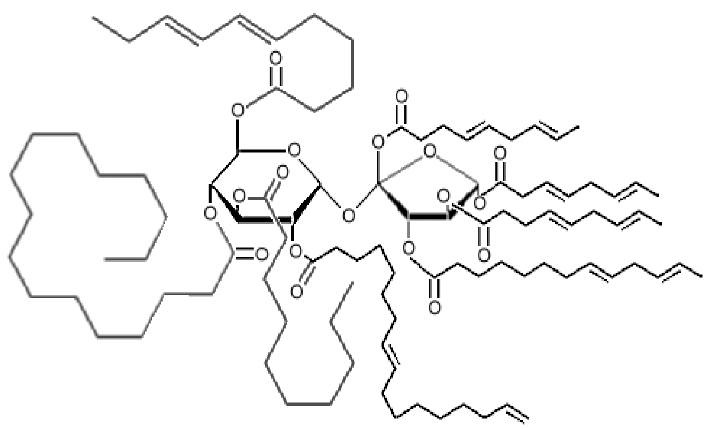


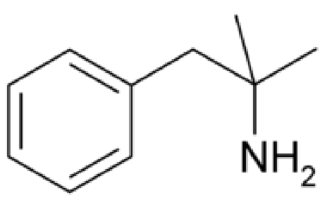
Figure 6 : Dextrin



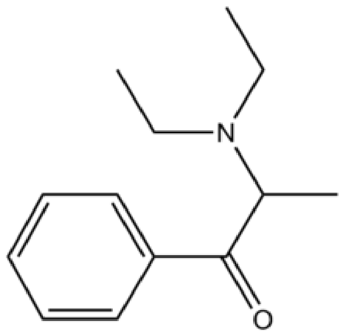
[7] Figure 7: Fatty Acid (Triglyceride)

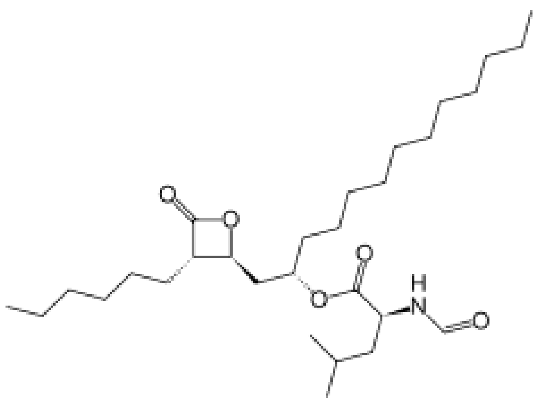


[8] Figure 8 : Olestra



[9] Figure 9 : Phentermine

10  Figure 10 : Diethylpropion

11  Figure 11: Orlistat

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