Chapter

The Sugars with the Potential to Prolong Human Life

Tomoya Shintani, Laura Lema-Perez and Hideya Shintani

Abstract

Sugar is the main source of energy for all cells in the human body. On the other hand, cells can also obtain energy from fats and proteins depending on conditions, although this metabolic process is more difficult and less common in cells. Sugar intake has increased in recent decades and is included in most of our dietary products. However, many studies indicate that sugar intake increases the prevalence of suffering from various harmful health conditions such as obesity. As a consequence, obesity is related to several chronic diseases such as hypertension, insulin resistance, and diabetes mellitus in humans. This is due to an excessive intake of sugars and sedentary lifestyles, causing a deterioration in the organs of our body, and consequently, reducing life expectancy. In this chapter, sugars that both shorten and lengthen life expectancy are presented. The latter are recent options that have emerged in order to continue sweetening our food in a healthier way, and would be new geroprotectors.

Keywords: Lifespan, healthy life, sugar, glucose metabolism

1. Introduction

Sugar is the main source of energy for the cells of the human body and is a nutrient that is abundantly found in nature and is widely used in the food processing industry. In the 1970s and 1980s, a strong association was found between cardiovascular disease, the number 1 cause of death in the world, and fat intake. For this reason, the food industry began to create low-fat but high-sugar consumer products. Today there is evidence that the high consumption of sugars in the recent decades has triggered a lot of chronic diseases that were not previously known, as diabetes mellitus. The appearance of chronic diseases such as diabetes mellitus has increased exponentially. Diabetes mellitus, e.g., is considered today a pandemic, due to it is one of the most prevalent not transmissible diseases in the world. The role sugar intake that is linked to aging is now relevant to the global chronic disease epidemic [1]. The global nonalcoholic fatty liver disease epidemic also has now become of major concern to diabetes [2].

Many scientific studies show that the increase in chronic diseases is due to excessive consumption of sugars and low-quality carbohydrates. This chapter presents in Section 2 the relationship between human life expectancy and sugar consumption, including a brief explanation of glucose metabolism in the human body. Later, Section 3 presents sugars as glucose, fructose, and galactose known as likely to shorten life with excessive intake. On the other hand, Section 4 presents sugar with potential to extend life expectancy like 2-deoxy-glucose, allulose, and glucosamine. Finally, the conclusions are presented.

2. Interaction of lifespan and sugar

2.1 Sugar consumption in human

Humans are always aging. The progress of aging and the life span are affected by environmental factors inside and outside the living body. One of the most promising environmental factors is oxidative stress. The free radical theory of aging is based on the idea that active oxygen, which is a causative agent of oxidative stress, oxidatively damages biomolecules and causes their accumulation to cause a decline in cell function, which causes aging [3]. Active oxygen is considered as a cause of various diseases as well as aging. Therefore, "antioxidant therapy" has been devised, which aims to treat diseases by controlling active oxygen as a toxic factor.

The generation of active oxygen is largely related to mitochondria. The main physiological role of mitochondria is to produce energy, or ATP. The ATP synthetic pathway includes anaerobic glycolysis that does not require oxygen and aerobic oxidative phosphorylation that requires oxygen [4]. The primary function of mitochondria is this oxidative phosphorylation. That is, by utilizing oxygen, more ATP is produced more efficiently than the glycolytic system. This oxidative phosphorylation is carried out by the electron transfer system existing in the inner mitochondrial membrane. About 100 kinds of proteins are involved in the electron transfer system, and various enzymes form a complex (Complex I to IV). In mitochondria, surprisingly, in addition to oxidative phosphorylation, metabolism such as ion channels, intracellular calcium homeostasis, fatty acid β-oxidation, neutral fat cycle, urea cycle, amino, fat, heme, purine, steroid and steroid hormone synthesis. It has various functions related to. Normally, 2 to 3% of electrons leak from the electron transport system, and the leaked electrons react with the most reactive oxygen molecule in the vicinity to produce superoxide.

Active oxygen is generated not only by external factors but also by internal factors. In mitochondria, active oxygen is produced as a by-product during the process of energy production. Some phagocytic cells produce active oxygen for the treatment of foreign substances such as bacteria. In some aspects, active oxygen is not necessarily an unfavorable existence for living things. Subsequent studies have revealed that active oxygen has a role as a physiologically active substance and a redox signal molecule [5, 6].

2.2 ROS generation and mitochondrial respiration

Complex I and Complex III are well known as the main generation sites of superoxide [7, 8]. Complex II also contributes to active oxygen produced from mitochondria [9]. Other mitochondrial enzymes that are not directly involved in the electron transport system also play a part in the production of mitochondrial active oxygen, and dihydroorotic acid oxidase is a by-product during the conversion of dihydroorotic acid to orotic acid and also the TCA (tricarboxylic acid) cycle. It has been reported that α-ketoglutarate dehydrogenase, which is an enzyme of *Escherichia coli*, also produces NADH/NAD+-dependent active oxygen [10, 11].

The mitochondrial oxidative metabolism of glucose is the most commonly known mechanism through which the ingestion of carbohydrates generates oxidative stress. Mitochondrial oxidative metabolism of glucose leads to the generation of reactive oxygen species (ROS). When glucose intake is high, glucose levels in the bloodstream rise, increasing many metabolic processes inside the cells regarding glucose metabolism, consequently increasing the ROS, and including the auto-oxidation, through the mitochondria. The mitochondrial respiration chain generates free radicals as a result of electron transport and depletion of the oxygen molecule.

Higher glucose consumption in the cell from the mitochondria causes a higher number of ROS [12]. Several studies [13] indicate that ROS, extremely reactive chemical molecules, are the major cause of the aging process in humans.

2.3 Hormesis

Hormesis is a biphasic response to exposure to increasing amounts of a substance [14]. Within the hormesis, there is generally a relatively favorable biological response to low exposures to toxic substances and other stressors. The concept of hormesis has been explored extensively with respect to its applicability is aging [15]. Because the survival capacity of any biological system is dependent on its defensive ability, exposing organisms to stress is expected to result in the adaptive response with various benefits. This idea has now gathered a large body of supportive evidence showing that repetitive mild stress exposure has anti-aging effects [16, 17]. Hormetic interventions have also been proposed at the clinical level [18], with a variety of stimuli, challenges and stressful actions, that aim to increase the dynamical complexity of the biological systems in humans [19].

ROS, which mentioned above, may perform an important lifespan-depending role as redox signaling molecules which transduce signals from the mitochondrial compartment to other compartments of the cell [20]. Increased temporarily formation of ROS within the mitochondria may cause an hormesis effect and reaction which induces increased stress resistance and a long-term reduction of oxidative stress. This type of reverse effect of the response to ROS stress has been named mitochondrial hormesis and is hypothesized to be responsible for the respective lifespan-extending capabilities of glucose restriction [20].

2.4 Sugar metabolism

Life is active. Energy is essential for activities. The most important source of energy for the cells of the human body is glucose. They create energy from glucose to stay alive and to carry out many metabolic processes in different organs and tissues. Humans have easy access to glucose. Glucose enters the human body through the mouth, where it begins to be processed by the amylases contained in saliva [21]. After that, the glucose travels up the esophagus to the stomach. Glucose and carbohydrates in general that reach the stomach do not undergo chemical or mechanical changes, since the enzymes that degrade them are not active at the acid pH that is in the stomach. The glucose then reaches the intestine, where it is absorbed into the bloodstream through the intestinal wall [21]. Then, glucose is metabolized in the liver thanks to the action of insulin. Excess glucose is stored as glycogen, while a quantity of glucose continues into the systemic circulation through the hepatic veins. Thus, glucose reaches all tissues to be used in cellular mitochondria as energy.

Glucose is absorbed quickly, whereas fructose is converted to glucose (10%) and the remaining 90% is absorbed as fructose. Sixty percent of the absorbed glucose is taken up by other tissues, such as the liver, 25% by the brain, 10% by muscle, and 5% by adipose tissue [22]. Meanwhile, almost all of the absorbed fructose is taken up by the liver. The glucose and fructose taken up by the liver is consumed in the glycolytic system, through the TCA cycle, and in ATP production, with the excess converted to glycogen and triglycerides. However, there is a major metabolic difference between glucose and fructose in the liver. Glucose is regulated by the insulin-dependent metabolic rate-limiting enzymes glucokinase, phospho-fructokinase, and glycogen synthase, but in the case of fructose, this regulatory mechanism does not work well. Fructose is mostly phosphorylated by fructokinase. However, there is no mechanism to control the phosphorylation of fructose and its subsequent

metabolism. Therefore, the influx of excess fructose into the liver leads to increased synthesis of triglycerides and release of triglycerides into the blood, resulting in hypertriglyceridemia because of the limited glycogen stores in the liver [23]. This process is especially active in diabetes mellitus with insufficient insulin action, because glycogen synthesis and ATP production are not as smooth as they could be.

3. Sugars with the potential to shorten human life

Glucose, fructose, and galactose are sugars that are likely to be short-lived with excessive intake. Specific characteristics of each one of them are presented in this section.

3.1 Glucose

Glucose is a simple sugar with the molecular formula $C_6H_{12}O_6$, as shown in **Figure 1**. Glucose is the most abundant monosaccharide, a subcategory of carbohydrates. Glucose is mainly made by plants and most algae during photosynthesis from water and carbon dioxide, using energy from sunlight, where it is used to make cellulose in cell walls, which is the most abundant carbohydrate [24]. In energy metabolism, glucose is the most important source of energy in all organisms. Glucose for metabolism is stored as a polymer, in plants mainly as starch and amylopectin, and in animals and humans as glycogen. Glucose circulates in the blood of animals as blood sugar. Glucose in the blood is the source of energy for cells throughout the body and is supplied through food intake and transported through the bloodstream.

Excessive glucose intake is directly linked to diabetes. Diabetes mellitus is one of the most prevalent chronic non-communicable diseases today. Type 2 diabetes mellitus (DM) is a progressive disease by uncontrolled plasma glucose levels. In the epidemiological study drawn from the general population, random glucose consumption showed a significant association with all-cause mortality, independent of main potential confounders [25]. Thus, random glucose measures are highly relevant to health risk assessment among people without known diabetes when fasting glucose or HbA1c is difficult to obtain.

DM results from a combination of factors affecting both insulin sensitivity and β-cell function. Chronic hyperglycemia imposes glucose toxicity on many cell types and is correlated with the myriad of DM-related complications [26]. Cells most vulnerable to the effects of prolonged elevated plasma glucose levels include pancreatic cells and vascular endothelial cells. The ensuing pancreatic dysfunction promotes decreased

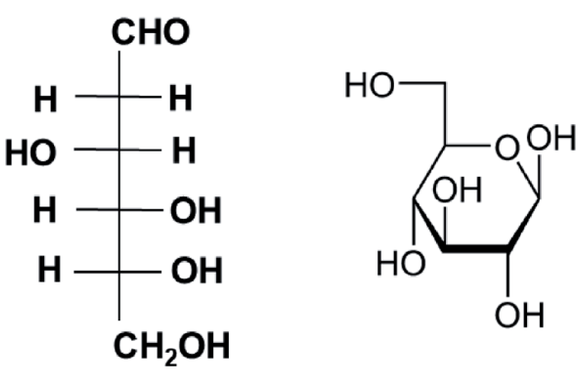

Figure 1.
Linear chemical structure (left) and Haworth projection structure (right) of a glucose molecule.

insulin secretion, further perpetuating the associated hyperglycemia. On the vascular endothelium, chronic hyperglycemia is correlated with some types of DM-related microvascular complications, including retinopathy and nephropathy [26].

3.2 Fructose

Fructose is contained in many fruits, vegetables, and honey. It is a monosaccharide with the same molecular formula as glucose ($C_6H_{12}O_6$), but with a different structure (see **Figure 2**), that is, it is an isomer of it. An increase intake of sugars, including fructose, in beverages is related to high prevalence of having obesity, type 2 DM, insulin resistance, hyperinsulinemia, and hypertension in humans. These chronic diseases without a good treatment or if they are not well controlled, cause a decrease in life expectancy. Nowadays, there is little scientific evidence for the fructose and its relationship with life expectancy in humans. It is known that fructose metabolism mainly occurs in the enterocytes (cells of the small intestine), hepatocytes (cells in the liver), and nephrons (cells in the kidneys) [27]. Nevertheless, few studies indicate that fructose could extend lifespan in some organisms as the nematode, fly and mice. This is due to life of many of those organisms, including yeast, is regulated by the insulin/IGF-1(Insulin-like Growth Factor-1)-signaling pathway [28].

On the other hand, high fructose corn syrup (HFCS) is commercially produced by isomerizing glucose to fructose. The taste quality of it is like sucrose and the price is affordable. This monosaccharide is a component of sucrose and is highly sweet (140% the sweetness of sucrose), leading to its frequent use in the food industry, particularly for beverage production. Thus, fructose consumption is common in the beverage industry, in which more sweetness is often needed [29]. In the field, fructose is used as a mixture of fructose and glucose, e.g., high fructose corn syrup, which is easy and inexpensive to manufacture from glucose. Thus, HFCS has been used for various foods such as beverages, confectionery, desserts and bakery. However, consumption of HFCS has been reported to be one of risk factors developing diabetes and obesity [30]. Sirtuin 1 is an anti-aging gene that becomes downregulated with relevance to the global chronic disease epidemic. Glucose and Fructose induce changes in Sirtuin 1 protein levels with relevance to induction of the metabolic syndrome and multiple organ disease syndrome [31]. Consumption of glucose and fructose should be carefully monitored with relevance to plasma Sirtuin 1 levels that now are connected to obesity, diabetes, NAFLD and neurodegenerative diseases [32]. Fructose induces gluconeogenesis and lipogenesis [33]. Excessive intake of fructose has been reported to result in short life [34].

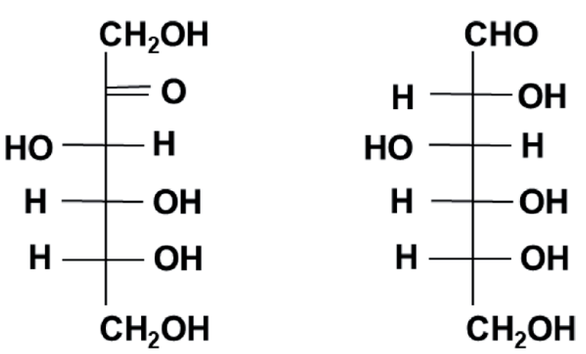

Figure 2.
Linear chemical structures of a fructose molecule (left) and a glucose molecule (right).

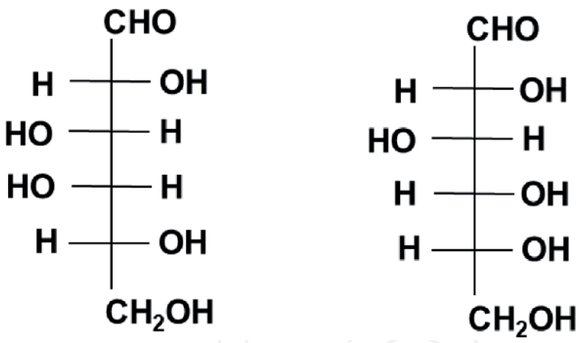

Figure 3.
Linear chemical structures of a galactose molecule (left) and a glucose molecule (right).

3.3 Galactose

Galactose is a C-4 epimer of glucose, as can be seen in **Figure 3**. Galactose, along with fructose and glucose, is an essential simple sugar included in the human diet. Galactose is a component of lactose, the disaccharide of which is contained in approximately 10% of milk. Lactose is a disaccharide that makes up around 3–7% of milk [35] and is derived from the condensation of galactose and glucose, which forms a β-glycosidic bond. Therefore, galactose can be consumed individually or in combination with other sugars in the form of more complex carbohydrates [36] to be digested and absorbed mainly in the small intestine into the bloodstream. In addition to being absorbed through the small intestine, some reports indicate that the human body can produce galactose endogenously [37] under some metabolic disorders associated with genetic mutations in enzymes of the Leloir pathway [38].

Many volumes of the disaccharides are produced annually as a by-product of the dairy industry [39]. Milk is consumed by people worldwide. However, lactose in milk may cause health problems in individuals with lactose intolerance [40, 41]. Thus, methods for lactose degradation in milk have been extensively studied [42, 43] and the lactose-free milk is produced and commercialized. In this case, studies have been conducted to assess blood glucose levels when lactose-free milk is consumed and a tendency to hyperglycemia was found 2 hours after consumption even in healthy people. The condition of hyperglycemia can be caused because lactose is ingested in its simplest forms, galactose, and glucose, and therefore it can be absorbed directly in the small intestine into the bloodstream, without going through digestion processes in the gastrointestinal tract. On the other hand, galactose can be produced industrially by lactase (β-galactosidase) derived from food microorganisms [44]. However, due to its low sweetness and limited research regarding its safety and functions [45], utilization of pure galactose in the food industry is not yet widespread [46]. Many animal studies have showed galactose induced accelerated aging in rodents [47, 48].

4. Sugars with the potential to prolong human life

2-Deoxy-glucose (2DG), allulose (AL), and glucosamine (GN) are sugars that are likely to be prolong life with intake. These monosaccharides would be new geroprotectors. This section describes a brief detail of all of them.

4.1 2-Deoxy-glucose

2DG is a glucose analog in which the 2-hydroxyl group is replaced by a hydrogen atom, as shown in **Figure 4**. 2DG is not at all metabolized via glycolysis and was

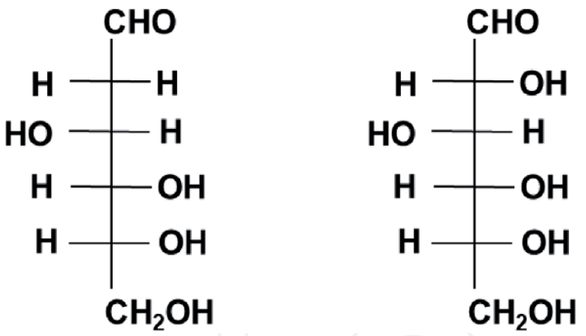

Figure 4.
Linear chemical structures of a 2-deoxy-glucose molecule (left) and a glucose molecule (right).

the first proposed calorie restriction mimetic [49]. It is considered to delay aging-related diseases and prolong the lifespan by suppressing glycolytic activity [50]. Schulz et al. [51] suggested a detailed mechanism for the 2DG longevity effect in *C. elegans* based on a hypothesis named as "mitochondrial hormesis". The hypothesis means that induction of mitochondrial metabolism may trigger a positive response to increased formation of ROS, leading to a hermetic increase in defense for stresses, resulting in decreased total stress levels. Inhibition of glycolysis by 2DG induces the utilization of stored lipid and mitochondrial respiration via AMPK (AMP-activated protein kinase). In a study comparing the effects of 2DG and calorie restriction in rodents, 2DG administration showed the same effects on locomotory activity, heart rate, and blood pressure as calorie restriction [52].

The same group of rodents demonstrated the protective effect of 2DG against glutamate excitotoxicity and upregulation of stress response proteins, in hippocampal cells [53]. Moreover, the same group demonstrated an improved behavioral outcome of 2DG treatment and reduced degeneration of dopaminergic neurons in a Parkinson's disease model [54], as well as decreases in proliferating cell nuclear antigen and bromodeoxyuridine-positive tumor cells [55]. On the other hand, a study in nematodes [56] found that the magnitude of gene expression values changes significantly when they are feeding with 2DG, the change is proportional to the age, but the most important thing is that their lifespan could be considerably extended.

Although 2DG shows the same effects as calorie restriction, few studies have examined its ability to extend lifespan. Rather, long-term 2DG ingestion induced heart vacuolation in rats and increased mortality [57]. However, 2DG is considered a potential caloric restriction mimetic due to it has effects on the metabolism that might regulate increases of the stress responses which protect against several aging processes, by improving longevity without a reduction or complete suppression of food intake. In this sense, Ingram et al. [58] shown that the use of 2DG reduces body temperatures, Dark et al. [59] report an increment of lethargy, Wan et al. [60] support a reduction of heart rate, and other studies indicate a declination of insulin and glucose blood levels [61, 62].

4.2 Allulose

Allulose (AL; psicose), a C-3 epimer of fructose (see **Figure 5**), is a rare hexose sugar present in a limited quantity in nature. In fact, this compound is isolated from natural products marketed as a functional sweetener with zero calories [62], easy to produce from d-fructose, in order to use it as a healthier sweetener in industrialized products.

In the previous decade, numerous studies showed that AL exhibits various activities, such as antihyperglycemic and antiobesity effects [63, 64], increment in the insulin sensitivity, attenuate cognitive impairment, delay diseases of aging,

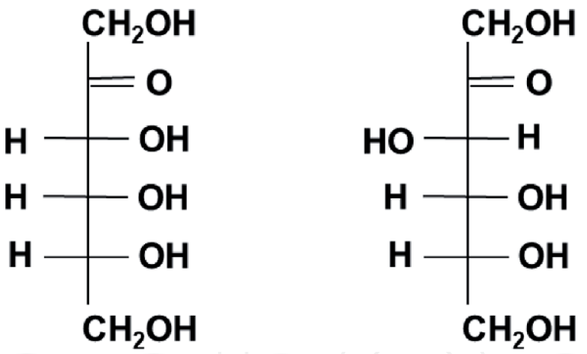

Figure 5.
Linear chemical structures of an allulose molecule (left) and a fructose molecule (right).

slow down cardiac aging, and prolong median life span [65, 66]. Toyoda et al. [67] reported that long-term administration of AL maintained glucose tolerance and insulin sensitivity in rats via hepatic glucokinase activation. Thus, AL is expected to be a potent antidiabetic sweetener. AL enters cells through glucose transporters and inhibits glycolysis, inducing the metabolism of stored fat and mitochondrial respiration via AMPK. Increased respiration causes temporary upregulation of ROS production, leading to increased antioxidant activity, oxidative stress resistance, and survival rates [68]. Although sirtuin is reported to be antiaging gene and a diagnostic marker to chronic disease [31], AL-mediated lifespan extension is independent of sirtuin gene.

In a clinical trial, AL was shown to be a geroprotector based on changes in biomarker levels such as glucose and body fat. A clinical trial using a standard meal confirmed that AL suppresses postprandial blood glucose levels [69]. Even a single dose of AL was reported to enhance postprandial fat oxidation in healthy humans [70]. Upon continuous intake of AL, the percentage of body fat and body fat mass significantly decreased, with no significant reduction in nutrient intake [71].

4.3 Glucosamine

GlcN is, a one of glucose derivatives, 2-amino-2-deoxy-glucose, as can be seen in **Figure 6**. GlcN is part of the structure of two polysaccharides, chitosan and chitin. GlcN is the fluid that surrounds the joints, but also is a constitutional unit of chitosan, which are contained in arthropods and cephalopods. In food industry, GlcN is manufactured by the hydrolysis of crustacean exoskeletons, which are mainly composed of chitin. GlcN is a dietary supplement that effectively prevents osteoarthritis in humans [72].

Weimer et al. reported the longevity effects of GlcN in nematodes and genetically modified mice [73]. The authors suggested that these effects were caused by impaired glucose metabolism. In contrast, the longevity effect of GlcN is reported to be required an autophagy for GlcN-induced lifespan extension [68], like that induced by other life-promoting sugars such as 2DG. Similar to 2DG, GlcN enters into cells through sugar transporters and inhibits glucose metabolism, inducing the oxidation of stored fat and intracellular respiration via an energy sensor (AMPK). Increased respiration can cause temporary production of ROS, leading to increases in antioxidative enzyme activity, stress resistance, and lifespan [74]. This effect is hormesis, mentioned above. Oral administration of GlcN has also been reported to affect carbohydrate metabolism and reduce fat in rodents [75] and contribute to enhanced oxidative stress resistance, followed by AMPK activation [74].

In a clinical trial, administration of GlcN improved vascular endothelial function by modulating the intracellular redox state [76]. According to an

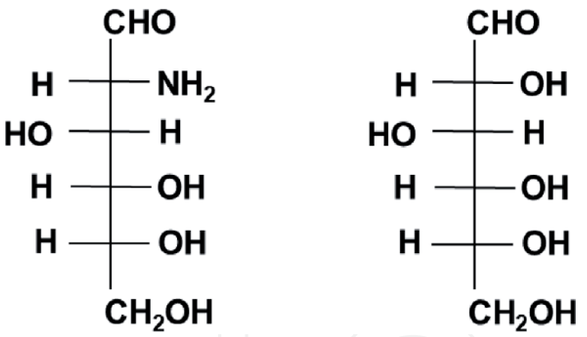

Figure 6.
Linear chemical structures of a glucosamine molecule (left) and a glucose molecule (right).

epidemiological study on consumers of various dietary supplements, the use of GlcN was associated with a decrease in total mortality [77]. Of further note is the latest large-scale cohort study reported in 2020. This study analyzed approximately 500,000 people and found that GlcN intake reduced the risk of cancer, heart disease, respiratory disease, digestive disease, and mortality [78].

5. Geroprotectors

"Geroprotector", whose technical term Ilya Mechnikov first used in 1908 [79], means "protecting against aging". The most important criterion of geroprotector is the ability to extend the lifespan of model organisms such as nematode fly and mice [80]. In 2001, Vladimir Anisimov suggested several types of geroprotectors using the most recognized theories of aging at that time as the typing criteria, which included antioxidants, neurotropic substances, hormones, antidiabetic drugs, immunomodulators, caloric restriction mimetics, and other substances and factors [81]. In the present, the various types would add longevity gene activators, including nicotinamide mononucleotide [82] and sirtuin activating compounds [83], as a new group to these conventional geroprotectors. Other new geroprotectors contain melatonin [84], and carnosine [85]. Among geroprotectors, the monosaccharides with the potential to prolong lifespan, mentioned in this chapter, is included in category of caloric restriction mimetics [49, 50]. This type of caloric restriction mimetics, whose action is considered glycolytic inhibition, mimics the anti-aging effects of long-term calorie restriction without requiring a change in eating habits [68].

6. Conclusion

Sugar consumption has increased since the 1990s when scientific studies found a strong association between fat consumption and cardiovascular problems. Since then, fats were almost sensed and sugars and carbohydrates were given priority. Sugar consumption has increased so much that it has triggered an enormous number of chronic diseases such as obesity and diabetes mellitus that, even today, have been declared a pandemic and a global emergency. Diseases caused by high sugar consumption generate a decline in the organs of the human body, which is closely linked to premature aging or a significant reduction in the quality of life of the people who suffer from them. In this regard, many studies have evidence that sugar intake to have effects in the human body associated with diseases as obesity and diabetes mellitus, however, little was until recently known about the effects

of sugars on lifespan. As mentioned in this chapter, sugars that both shorten and lengthen life expectancy was presented. The good options with antiaging effect of the sugars have emerged in order to continue sweetening our food in a healthier way. It would be new geroprotectors in the near future.

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Conflict of interest

The authors declare no competing financial interest. Tomoya Shintani is an employee of a private enterprise (Japan). However, the company provided no financial support for writing this book chapter.

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References

[1] Martins I: Anti-Aging Genes Improve Appetite Regulation and Reverse Cell Senescence and Apoptosis in Global Populations. Advances in Aging Research 2016; 5: 9-26. DOI: 10.4236/aar.2016.51002.

[2] Martins I: Insulin Therapy and Autoimmune Disease with Relevance to Nonalcoholic Fatty Liver Disease. Non Alcoholic Fatty Liver Disease. An Update. IntechOpen. 2018.

[3] Harman D: Aging: A theory based on free radical and radiation chemistry. J Gerontol 1956; 11: 298-300.

[4] Peek CB, Levine DC, Cedernaes J, Taguchi A, Kobayashi Y, Tsai SJ, Bonar NA, McNulty MR, Ramsey KM, Bass J: Circadian Clock Interaction with HIF1α Mediates Oxygenic Metabolism and Anaerobic Glycolysis in Skeletal Muscle. Cell Metab 2017; 25: 86-92. DOI: 10.1016/j.cmet.2016.09.010.

[5] Zorov, Dmitry B et al: "Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release." Physiological reviews 2014; 94: 909-950. DOI:10.1152/physrev.00026.2013.

[6] Owusu-Ansah E, Banerjee: Reactive oxygen species prime Drosophila haematopoietic progenitors for differentiation. Nature 2009; 461: 537-541. DOI: https://doi.org/10.1038/nature08313

[7] Takeshige K, Minakami S: NADH- and NADPH dependent formation of superoxide anions by bovine heart submitochondrial particles and NADH ubiquinone reductase preparation. Biochem J 1979; 180: 129-135.

[8] Trumpower B L: The protonmotive Q cycle. Energy transduction by coupling of proton translocation to electron transfer by the cytochrome bc1 complex. J Biol Chem. 1990; 265: 11409-11412.

[9] McLennan HR, Degli Esposti M: The contribution for mitochondrial respiratory complexes to the production of reactive oxygen species. J Bioenerg Biomembr 2000; 32: 153-162.

[10] Forman HJ, Kennedy J: Dihydro orotate dependent superoxide production in rat brain and liver: a function of the primary dehydrogenase. Arch Biochem Biophys 1976; 173: 219-224.

[11] Tretter L, Adam-Vizi V: Generation of reactive oxygen species in the reaction catalyzed by α-ketoglutarate dehydrogenase. J Neurosci. 2004; 24: 7771-7778.

[12] Piotrowska A, Bartnik E: The role of reactive oxygen species and mitochondria in aging. Postepy Biochem. 2014; 60: 240-247.

[13] Ha H, Lee HB: Reactive oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. Kidney Int Suppl 2000; 77: S19-25. DOI: 10.1046/j.1523-1755.2000.07704.x.

[14] Mattson MP: Hormesis Defined. Ageing Research Reviews. 2007; 7: 1-7. DOI:10.1016/j.arr.2007.08.007.

[15] Rattan SI: Principles and practice of hormetic treatment of aging and age-related diseases. Human & Experimental Toxicology 2008; 27: 151-4. DOI:10.1177/0960327107083409

[16] Rattan, Suresh IS: Hormesis in aging. Ageing Research Reviews 2008; 7: 63-78. DOI:10.1016/j.arr.2007.03.002

[17] Gems D, Partridge L: "Stress-Response Hormesis and Aging: "That which Does Not Kill Us Makes Us Stronger"". Cell Metabolism 2008; 7: 200-203. DOI:10.1016/j.cmet.2008.01.001

[18] Kyriazis M: "Clinical Anti-Aging Hormetic Strategies". Rejuvenation Research 2005; 8: 96-100. DOI:10.1089/rej.2005.8.96

[19] Kyriazis M: "Practical applications of chaos theory to the modulation of human ageing: Nature prefers chaos to regularity". Biogerontology 2003; 4: 75-90. DOI:10.1023/A:1023306419861

[20] Ristow M, Zarse K: "How increased oxidative stress promotes longevity and metabolic health: The concept of mitochondrial hormesis (mitohormesis)". Experimental Gerontology 2010; 45: 410-8. DOI: 10.1016/j.exger.2010.03.014

[21] Lema-Perez L, Garcia-Tirado J, Builes-Montaño C, Alvarez H: Phenomenological-Based model of human stomach and its role in glucose metabolism. Journal of Theoretical Biology 2019; 460: 88-100.

[22] Mergenthaler P: "Sugar for the brain: the role of glucose in physiological and pathological brain function." Trends in neurosciences 2013; 36: 587-597. DOI:10.1016/j.tins.2013.07.001

[23] Ter H, Kasper W, Mireille JS: "Fructose Consumption, Lipogenesis, and Non-Alcoholic Fatty Liver Disease." Nutrients 2017; 9: 981. DOI:10.3390/nu9090981

[24] Abraham JD, Joseph K, David MW, editors. Handbook of Biodegradable Polymers. 1st ed. Boca Raton: CRC Press; 1998. 275p. ISBN: 978-1-4200-4936-7.

[25] Jens B, Christin H, Rebecca P, Yong D, Christa S-N: Association between random glucose and all-cause mortality: findings from the mortality follow-up of the German National Health Interview and Examination Survey 1998. BMC Endocr Disord 2018; 18: 95. DOI: 10.1186/s12902-018-0319-2.

[26] Carlos C: Chronic Hyperglycemia and Glucose Toxicity: Pathology and Clinical Sequelae. Postgraduate medicine 2012; 124: 90-7. DOI: 10.3810/pgm.2012.11.2615.

[27] Tappy L and Rosset R: Health outcomes of a high fructose intake: the importance of physical activity. J Physiol 2019; 597: 3561-3571. DOI: https://doi.org/10.1113/JP278246

[28] Barbieri M, Bonafe M, Franceschi C, Paolisso G: Insulin/IGF-I-signaling pathway: an evolutionarily conserved mechanism of longevity from yeast to humans. Am J Physiol Endocrinol Metab 2003; 285: E1064–E1071.

[29] Park YK, Yetley EA: Intakes and food sources of fructose in the United States. Am J Clin Nutr 1993; 58: 737S–747S.

[30] Gross S, Li L, Ford S, Liu S: Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: An ecologic assessment. Am. J Clin Nutr 2004; 79: 774-779.

[31] Martins I: "Sirtuin 1, a Diagnostic Protein Marker and its Relevance to Chronic Disease and Therapeutic Drug Interventions". EC Pharmacology and Toxicology 2018; 6; 209-215.

[32] Martins I: Single Gene Inactivation with Implications to Diabetes and Multiple Organ Dysfunction Syndrome. J Clin Epigenet 2017; 3: 24. DOI: 10.21767/2472-1158.100058

[33] Caton PW, Nayuni NK, Khan NQ, Wood EG, Corder R: Fructose induces gluconeogenesis and lipogenesis through a SIRT1-dependent mechanism. J Endocrinol 2011; 208: 273-283. DOI: 10.1530/JOE-10-0190.

[34] Collino M: High dietary fructose intake: Sweet or bitter life? World J Diabetes. 2011; 15: 77-81. DOI: 10.4239/wjd.v2.i6.77

[35] Ammam M, Fransaer J: Two-enzyme lactose biosensor based on β-galactosidase and glucose oxidase deposited by AC-electrophoresis: Characteristics and performance for lactose determination in milk. Sens. Actuators B Chem 2010; 148: 583-589.

[36] Acosta PB, Gross KC: "Hidden sources of galactose in the environment," European Journal of Pediatrics 1995; 154: S87–S92.

[37] Berry GT, Nissim I, Lin Z, Mazur AT, Gibson JB, and Segal S: "Endogenous synthesis of galactose in normal men and patients with hereditary galactosaemia," The Lancet 1995; 8982: 1073-1074.

[38] Lai K, Elsas JL, Wierenga JK: "Galactose toxicity in animals," IUBMB Life 2009; 61: 1063-1074.

[39] Yang ST, Silva EM: Novel products and new technologies for use of a familiar carbohydrate, milk lactose. J Dairy Sci 1995; 78: 2541-2562.

[40] Kretchmer N: Lactose and lactase. Sci Am 1972; 227: 70-79.

[41] Heyman MB: Lactose intolerance in infants, children, and adolescents. Pediatrics 2006, 118, 1279-1286.

[42] Dekker JP, Koenders D, Bruins JM: Lactose-free dairy products: Market developments, production, nutrition and health benefits. Nutriets 2019; 11: 551.

[43] Hodges KJ, Cao S, Cladis PD, Weaver MC: Lactose intolerance and bone health: The challenge of ensuring adequate calcium intake. Nutriets 2019; 11: 718.

[44] Nakanishi K, Matsuno R, Torii K, Yamamoto K, Kamikubo T: Properties of immobilized β-d-galactosidase from Bacillus circulans. Enzym Microb Technol 1983; 5: 115-120.

[45] Michaëlsson K, Wolk A, Langenskiöld S, Basu S, Lemming EW, Melhus H, Byberg L: Milk intake and risk of mortality and fractures in women and men: Cohort studies. BMJ 2014; 349: g6015.

[46] Lai K, Elsas LJ, Wierenga KJ: Galactose toxicity in animals. IUBMB Life 2009; 61: 1063-1074.

[47] Ho SC, Liu JH, Wu RY: Establishment of the mimetic aging effect in mice caused by D-galactose. Biogerontology 2003; 4: 15-18. DOI: https://doi.org/10.1023/A:1022417102206

[48] Azman KF, Zakaria R: d-Galactose-induced accelerated aging model: an overview. Biogerontology 2019; 20: 763-782. DOI: https://doi.org/10.1007/s10522-019-09837-y

[49] Lane M, Ingram DK, Roth G: 2-Deoxy-d-Glucose Feeding in Rats Mimics Physiologic Effects of Calorie Restriction. J Anti Aging Med 2009; 1: 327-337.

[50] Roth SG, Lane MA, Ingram DK: Caloric restriction mimetics: The next phase. Ann N Y Acad Sci 2005; 1057: 365-371.

[51] Wang A, Mouser J, Pitt J, Promislow D, Kaeberlein M: Rapamycin enhances survival in a Drosophila model of mitochondrial disease. Oncotarget 2016; 7: 80131-80139.

[52] Wan R, Camandola S, Mattson MP: Intermittent fasting and dietary supplementation with 2-deoxy-d-glucose improve functional and metabolic cardiovascular risk factors in rats. FASEB J 2003; 17: 1133-1134.

[53] Lee J, Bruce-Keller AJ, Kruman Y, Chan SL, Mattson MP: 2-Deoxy-d-glucose protects hippocampal neurons against excitotoxic and oxidative injury: Evidence for the involvement of stress proteins. J Neurosci Res 1999; 57: 48-61.

[54] Duan W, Mattson MP: Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease. J Neurosci Res 1999; 57: 195-206.

[55] Singh S, Pandey S, Bhatt AN, Chaudhary R, Bhuria V, Kalra N, Soni R, Roy BG, Saluja D, Dwarakanath BS: Chronic dietary administration of the glycolytic inhibitor 2-deoxy-d-glucose (2-DG) inhibits the growth of implanted Ehrlich's ascites tumor in mice. PLoS ONE 2015; 10: e0132089.

[56] Priebe S, Menzel U, Zarse K, Groth M, Platzer M, Ristow M, Guthke R: Extension of life span by impaired glucose metabolism in *Caenorhabditis elegans* is accompanied by structural rearrangements of the transcriptomic network. Plos One 2013; 30: e77776.

[57] Minor RK, Smith DL, Sossong AM, Kaushik S, Poosala S, Spangler EL, Roth GS, Lane M, Allison DB. de Cabo R et al: Chronic ingestion of 2-deoxy-d-glucose induces cardiac vacuolization and increases mortality in rats. Toxicol. Appl. Pharmacol. 2010; 243: 332-339.

[58] Ingram DK, Roth GS, Lane MA, Ottinger MA, Zou S, de Cabo R, Mattison JA: The potential for dietary restriction to increase longevity in humans: extrapolation from monkey studies. Biogerontology 2006; 7: 143-148.

[59] Dark J, Miller DR, Zucker I: Reduced glucose availability induces torpor in Siberian hamsters. Am J Physiol 1994; 267: R496–R501.

[60] Wan R, Camandola S, Mattson MP: Intermittent fasting and dietary supplementation with 2-deoxy-D-glucose improve functional and metabolic cardiovascular risk factors in rats. FASEB J 2003; 17:1133-1134.

[61] Lane MA, Ingram DK, Roth GS: 2-Deoxy-D-glucose feeding in rats mimics physiological effects of calorie restriction. J Anti-Aging Med 1998;1: 327-337.

[62] Iida T, Hayashi N, Yamada T, Yoshikawa Y, Miyazato S, Kishimoto Y, Okuma K, Tokuda M, Izumori K: Failure of d-psicose absorbed in the small intestine to metabolize into energy and its low large intestinal fermentability in humans. Metabolism 2010; 59: 206-214.

[63] Mooradian AD, Smith M, Tokuda M: The role of artificial and natural sweeteners in reducing the consumption of table sugar: A narrative review. Clin Nutr ESPEN 2017; 18: 1-8.

[64] Hossain A, Yamaguchi F, Matsuo T, Tsukamoto I, Toyoda Y, Ogawa M, Nagata Y, Tokuda M: Rare sugar d-allulose: Potential role and therapeutic monitoring in maintaining obesity and type 2 diabetes mellitus. Pharmacol Ther 2015; 155: 49-59.

[65] Pongkan W, Jinawong, K., Pratchayasakul, W. et al: d-allulose provides cardioprotective effect by attenuating cardiac mitochondrial dysfunction in obesity-induced insulin-resistant rats. Eur J Nutr 2020; DOI: https://doi.org/10.1007/s00394-020-02394-y

[66] Pratchayasakul W, Jinawong K, Pongkan W, Jaiwongkam T, Arunsak B, Chunchai T, Tokuda M, Chattipakorn N, Chattipakorn CS: Not only metformin, but also D-allulose, alleviates metabolic disturbance and cognitive decline in prediabetic rats. Nutritional Neuroscience 2020: DOI: 10.1080/1028415X.2020.1840050

[67] Toyoda Y, Mori S, Umemura. N, Futamura N, Inoue H, Hata T, Miwa I, Murao K, Nishiyama A, Tokuda M: Suppression of blood glucose levels by d-psicose in glucose tolerance test in

diabetic rats. Jpn Pharmacol Ther 2010; 38: 261– 269.

[68] Ingram DK, Roth GS: Glycolytic inhibition: an effective strategy for developing calorie restriction mimetics. GeroScience 2020; DOI: https://doi.org/10.1007/s11357-020-00298-7

[69] Hayashi, N, Iida T, Yamada T, Okura K, Takehara I, Yamamoto T, Yamada K, Tokuda M: Study on the postprandial blood glucose suppression effect of d-psicose in borderline diabetes and the safety of long-term ingestion by normal human subjects. Biosci Biotechnol Biochem 2010; 74: 510-519.

[70] Kimura T, Kanasaki A, Hayashi N, Yamada T, Iida T, Nagata Y, Okuma K: d-Allulose enhances postprandial fat oxidation in healthy humans. Nutrition 2017; 43-44: 16-20.

[71] Han Y, Kwon EY, Yu M, Lee S, Kim HJ, Kim SB, Kim Y, Choi MS: A preliminary study for evaluating the dose-dependent effect of d-allulose for fat Mass reduction in adult humans: A randomized, double-blind, placebo-controlled trial. Nutrients 2018; 10:160. DOI: 10.3390/nu10020160.

[72] Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JE, Gossett C: Long-term effects of glucosamine sulphate on osteoarthritis progression: A randomised, placebo-controlled clinical trial. Lancet 2001; 357: 251-256.

[73] Weimer S, Priebs J, Kuhlow D, Groth M, Priebe S, Mansfeld J, Merry TL, Dubuis S, Laube B, Pfeiffer AF et al: d-Glucosamine supplementation extends life span of nematodes and of ageing mice. Nat Commun 2014; 5: 3563.

[74] Tim JS, Kim Z, Anja V, Nadine U, Marc B, Michael R: Glucose restriction extends *Caenorhabditis elegans* life span by inducing mitochondrial respiration and increasing oxidative stress. Cell Metab 2007; 6: 280-293. DOI: 10.1016/j.cmet.2007.08.011.

[75] Barrientos C, Racotta R.; Quevedo L: Glucosamine attenuates increases of intraabdominal fat, serum leptin levels, and insulin resistance induced by a high-fat diet in rats. Nutr Res 2010; 30: 791-800.

[76] Katoh A, Kai H, Harada H, Niiyama H, Ikeda H: Oral administration of glucosamine improves vascular endothelial function by modulating intracellular redox state. Int. Heart J 2017; 58: 926-932.

[77] Pocobelli G, Kristal AR, Patterson RE, Potter JD, Lampe JW, Kolar A, Evans I, White E: Total mortality risk in relation to use of less-common dietary supplements. Am J Clin Nutr 2010; 91: 1791-1800.

[78] Zhi-Hao L, Xiang G, Vincent CHC et al: Associations of regular glucosamine use with all-cause and cause-specific mortality: a large prospective cohort study. Annals of the Rheumatic Diseases 2020; 79: 829-836.

[79] Metchnikoff E, Mitchell PC: The prolongation of life: optimistic studies. Putnam's Sons 1908, New York & London.

[80] Moskalev A, Chernyagina E, Kudryavtseva A, Shaposhnikov M: Geroprotectors: A Unified Concept and Screening Approaches. Aging Dis 2017; 8: 354-363. DOI: 10.14336/AD.2016.1022.

[81] Anisimov VN: Life span extension and cancer risk: myths and reality. Exp Gerontol 2001; 36: 1101-1136.

[82] Mills KF, Yoshida S, Stein LR, Grozio A, Kubota S, Sasaki Y, Redpath P, Migaud ME, Apte RS, Uchida K,

Yoshino J, Imai SI: Long-Term Administration of Nicotinamide Mononucleotide Mitigates Age-Associated Physiological Decline in Mice. Cell Metab 2016; 24:795-806. DOI: 10.1016/j.cmet.2016.09.013.

[83] Hubbard BP, Sinclair DA: Small molecule SIRT1 activators for the treatment of aging and age-related diseases. Trends Pharmacol Sci 2014; 35: 146-54. DOI: 10.1016/j.tips.2013.12.004.

[84] Anisimov VN, Popovich IG, Zabezhinski MA, Anisimov SV, Vesnushkin GM, Vinogradova IA: Melatonin as antioxidant, geroprotector and anticarcinogen. Biochim Biophys Acta 2006;1757:573-589. DOI: 10.1016/j.bbabio.2006.03.012.

[85] Boldyrev AA, Stvolinsky SL, Fedorova TN, Suslina ZA: Carnosine as a natural antioxidant and geroprotector: from molecular mechanisms to clinical trials. Rejuvenation Res 2010; 13: 156-158. DOI: 10.1089/rej.2009.0923.