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The "sugar dilemma"

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Type 2 diabetes mellitus is characterized by insulin resistance and elevated blood glucose levels. Treatment protocols generally include dietary restriction of sugar, as well as drugs aiming at a reduction of blood glucose, mainly by activating the insulin system or supplementing insulin. This established approach does not take into account the outstanding physiological role of glucose as a key molecule in metabolism. Glucose is crucial to meet the high energy demand of the brain, which depends on it as an exclusive nutrient. Insulin independent glucose transporters GLUT1 import glucose into the brain. Reduction of blood glucose, as in current treatment concepts, may lead to energy deficiency in the brain and consecutively to worsening of – possibly already impaired – neurocognitive function. Reduced cell membrane fluidity of the vascular endothelium of the blood-brain-barrier (BBB) – due to malnutrition and/or aging – is considered a major factor in pathogenesis of the cerebral metabolic syndrome, which is a key step in neurodegeneration. Under this aspect we suggest a novel approach to prophylaxis and treatment focusing on a sufficient supply of glucose to the brain.

1. Introduction

Obesity is a steadily increasing phenomenon in human society. It has been recognized as a critical starting point for life-threatening diseases. Measures to overcome the problem range from diet to bariatric surgery. Obesity is a frequently discussed topic in conversations, guidebooks and media, resulting in a wide variety of dietary recommendations. Public, academic and commercial initiatives raise awareness for the problem. Obesity is also an important field of scientific and clinical research. Thus, a recent clinical study has connected obesity to industrial food, revealing that ultra-processed products cause increased calorie intake and weight gain (Poti et al. 2017). High sugar concentrations in soft drinks are one of the appetizing options in industrial food. Thus, "sugar avoidance" has become a target in anti-obesity initiatives. However, such sugar-related initiatives generally do not specify the term "sugar". "Sugar is poison" is just one of many misleading arguments.

Type 2 diabetes mellitus is one of the secondary diseases of obesity. Elevated blood glucose levels and high levels of glycated hemoglobin (HbA_{1c}) are the most important diagnostic parameters for impending diabetes. At the same time, glycation is considered as the main reason for vascular damage in connection with diabetes and atherosclerosis. The reduction of blood sugar levels remains the common goal of most measures and pharmacotherapeutic efforts in diabetes therapy. Although type 1 and type 2 diabetes are based on different pathomechanisms, both disease entities are known to finally result in a lack of insulin effects. In type 1 diabetes, an absolute deficiency of insulin is common, whereas patients with type 2 diabetes suffer from insulin resistance and a relative insulin deficiency (Kahn et al. 2006). However, the situation with the "bad" blood glucose is by far not as straightforward as it might seem. A dreadful complication in diabetes patients requiring insulin therapy is hypoglycemia due to insulin overdose – a life threatening state due to the constantly high demand of the brain for glucose (Donnelly et al. 2005).

Regarding the evolution of metabolic systems, glucose is an essential and central biochemical constituent. It is degraded in cells to provide essential metabolites. A secured and precisely regulated transport of glucose over membranes is essential for cells in all organs and tissues, particularly in the brain due to the required high energy demands (Duelli and Kuschinsky 2001). Not surprisingly, the lack of glucose is the trigger for mitochondrial apoptosis (Rehni et al. 2015). The complex regulation of glucose is – at least in our opinion – not perfectly understood. Reduction of blood glucose levels in type 2 diabetic patients might be an insufficient approach to cope with the dysfunction of this highly regulated fundamental physiological system (Aronoff et al. 2004).

Lipid membranes surrounding the cells are crucial for metabolic function. Receptors and transporters at these membranes organize the cellular metabolism in a perfectly organized signaling and transport system. Most nutrients, including glucose, cross cell membranes via active transport over the vascular endothelium. It is evident that an impairment of membrane function, starting with the loss of membrane fluidity, will have a negative effect on cellular nutrient supply. Atherosclerosis, the metabolic syndrome and secondary diseases are consequences of this impairment (Grundy et al. 2004; Sorci-Thomas and Thomas 2016). Dysfunction of vascular membranes becomes particularly critical at the blood-brain barrier (BBB), which is the very tight vascular membrane system separating the brain from the blood (Pilon 2016; Weiss et al. 2009). The brain depends on glucose as the almost exclusive source of energy (Fehm et al. 2006). Due to the permanently high demand of the brain for glucose, transporters at the BBB are independent from insulin signaling (Kumagai 1999). Therefore, insulin substitution does not considerably contribute to the glucose transport across the impaired BBB. These characteristics of cerebral metabolism result in a dilemma for aging people that must keep their blood glucose levels low to avoid diabetes, although they are at risk of suffering from glucose deficiency in the brain, which potentially contributes to neurodegeneration.

In view of the fact that undifferentiated recommendations for "sugar avoidance" might result in severe negative consequences, it is the goal of this publication to contribute to a more differentiated view on "sugars" and "sweetness" as well as to point towards the eminent role of glucose as a key molecule of life.

2. Glucose – a primordial molecule of life

Glucose belongs to the class of carbohydrates that together with proteins, fats and nucleic acids make up the major constituents of living matter. The term "carbohydrate" formally describes these compounds as hydrates (H_2O) of carbon (C). The monomer of this class is formaldehyde, the dimer is glycolaldehyde and the trimer is glyceraldehyde, which is the simplest asymmetric sugar. D-Glyceraldehyde has been the stereochemical reference of all sugars and chiral molecules. Formaldehyde and glycolaldehyde have been detected in interstellar matter. It has been shown that trimerization of glycolaldehyde results in a mixture of a few sugars, in which glucose is the dominating compound (Noe et al. 2013). Beyond that, stereo-electronic effects allow a mechanistic interpretation that even D-glucose, which turns polarized light to the right direction and is therefore also named dextrose, may be generated in straightforward self-constitution reaction under prebiotic conditions (Noe et al. 2013)

Glucose is not only a biomolecule but also a primordial fundament of evolution. The structural importance of glucose can be seen ubiquitously, e.g., in living plants and wooden materials. Cellulose and starch, the two linear polymers of glucose are the most abundant natural products. At the same time, glucose is known to be the main energy source of cells. This fundamental role is also reflected in the bio-ecological energy cycle, in which plants convert carbon dioxide and water to glucose generating oxygen, whereas animals "burn" glucose to carbon dioxide and water consuming oxygen. However, glucose is not just a supplier of cellular energy. Glucose is also an important signaling molecule. The glucose-mediated physiological response to sweet taste is of eminent importance. It is *the reward* of the brain to appropriate food intake.

3. Obesity

Growing standards of life in the industrialized world come along with less physical activity and increased food intake. Thus, obesity has become one of the most relevant issues of public health with overnutrition as a major theme. Human nutrition is mainly provided by carbohydrates. A reduced intake of starch – e.g. by slightly reduced eating of potatoes or bread – would be a more effective approach in calorie restriction than fundamental sugar avoidance.

Nevertheless, sugar is definitely an important issue in terms of obesity. However, the situation is by far more complex than it is let on by industry, media and popular science. Certainly, a lack of energy generates the feeling of hunger by precise neuronal cascades (Chen et al. 2016) that interact with hormone fluctuations (e.g., ghrelin and leptin), chemical senses and mechanic conditions like gastric contractions (Andermann and Lowell 2017). However, easy availability of food in industrial countries has decoupled the feeling of "physical" hunger from food intake. Hunger – need for food, and satiety – absence of hunger, are sensations. Nevertheless, in industrial societies appetite has become the main reason for food intake. The increased tendency to develop obesity in connection with industrial food comes along with the commercially understandable goal to sell products that taste well and raise the appetite. There is a long list of appetizers including glutamic acid, salt, sweeteners and several other ingredients that stimulate the consumer's appetite. The sensation of appetite is regulated by complex neuronal circuits that are influenced by various factors like visual and olfactory stimuli or low energy levels that activate peripheral (e.g., sensory nerves from the gastrointestinal tract) (Schwartz 2000) and central nervous regions, e.g., the hypothalamus (especially in terms of energy homeostasis) (Lawrence et al. 1999), or components of the limbic system (brain areas modulating reward processing and motivation) (Wu et al. 2012). Thus, not only flavor enhancement raises appetite, but also smell, sight, touch and sound. Appealing foods stimulate appetite even in absence of hunger. Therefore, appetite is the main drive for overnutrition.

Appetite and eating behavior are strongly influenced by psychological factors, potentially resulting in severe eating disorders like anorexia nervosa or polyphagia. Additionally, stress plays an important role. Chronic stress eventually increases appetite levels and induces increased food intake (Chao et al. 2017). Altogether, changes in lifestyle, psychological factors and increased availability of highly processed food explain the dramatic increase of obesity and a series of secondary diseases.

4. The metabolic syndrome

The term *metabolic syndrome* describes the cluster of obesity, elevated blood lipid levels, hypertension and impaired glucose tolerance (Grundy et al. 2004). It represents the common pathologic starting point for secondary diseases like diabetes mellitus, myocardial infarction and stroke. Its growing global prevalence comes along with the continuous increase of obesity based on unfavorable living conditions and eating habits. Summing up these conditions into one clinical picture has proven its worth in respect of prevention and therapy (Mendrick et al. 2018).

Etiology and treatment of hypertonia follow basically the mechanistic assumption that stiff endothelial membranes are the reason for dysfunctional pressure regulation. All mammalian cells are surrounded by a cell membrane largely consisting of a phospholipid bilayer. The lipid bilayer is a fundamental element of cellular life surrounding the cell like a fence and defining its shape. Like stacks in a fence, phosphocholine esters of long chain fatty acids aggregate side by side by the force of van der Waals bonds, thus forming a membrane layer. Unsaturated natural fatty acids disturb the high stacking order, thereby enhancing the fluidity of membranes, while cholesterol and saturated fatty acid esters stabilize the membranes and make them less fluid (Yeagle 1985). This holds especially true for the endothelial cells making up the internal wall of blood vessels. A wide range of ion channels, transporters, hormone receptors and neurotransmitters, as well as specific epitopes for cellular interaction and signaling are integrated in these membranes. Their functionality essentially depends on the membrane fluidity and therefore on the appropriate ratio between phospholipids and cholesterol. An over-accumulation of cholesterol and unfavorable fatty acids – e.g., by nutritional misbehavior – leads to stiffening of the membrane (Maxfield and Tabas 2005) and results in endothelial cells with impaired membrane function (Esposito et al. 2004). Reduced membrane fluidity provides a reasonable explanation for the significance of endothelial cell membrane dysfunction as an early step in the pathogenesis of the metabolic syndrome.

Consequently, therapeutic options to treat hypertonia comprise the reduction of the liquid volume within the system by forced diuresis, vessel dilatation and concomitant reduction of cardiac load. The inflammatory process of atherosclerosis further aggravates membranous dysfunction of endothelial cells and triggers the pathologic processes (Pilon 2016; Sorci-Thomas and Thomas 2016). It plays a central role in the progression of the metabolic syndrome, resulting in a damage to blood vessels affecting all vascular layers and further promoting hypertonia (Van Gaal et al. 2006). Infarction and stroke are ultimate consequences of this process. The underlying pathogenetic steps are well described and various components, such as fatty streaks and foam cells have been found in atherosclerotic vessels. Both prevention of the metabolic syndrome and therapy of hypertension are meant to avoid myocardial infarction and stroke as secondary events (Grundy et al. 2004; Isomaa et al. 2001). Although further details on the mechanisms of inflammation and infection, respectively, are still to be clarified, the etiology of both diseases and their relation to vascular endothelial dysfunction is basically well understood (Laurent and Boutouyrie 2015; Sorci-Thomas and Thomas 2016).

5. Basic insights in glucose metabolism and type 2 diabetes

In healthy humans, carbohydrates are broken down to monosaccharides including glucose molecules in the small intestine. Then, these molecules are taken up across the layers of the intestinal wall and transported into the liver, where they are either metabolized and released into the blood system or stored (Aronoff et al. 2004). As a consequence, the blood glucose level is rising and the

pancreas releases the peptide hormone insulin that regulates the uptake of glucose into the cells by targeting insulin receptors on the cell surface.

The absorption of glucose from the circulating blood into cells is not effected by diffusion, but by active transport with a set of glucose transporters, mostly the well-characterized glucose transporters GLUT1 to GLUT4 (Wright et al. 2007). In peripheral target cells, such as skeletal and cardiac muscle cells and in adipose tissue, the transport is effectuated by GLUT4. Expression and presentation of this transporter is regulated by the glucose-insulin system (Saltiel and Kahn 2001). In response to their current demand, cells express membranous insulin receptors. Activated by insulin, these receptors induce the expression of glucose transporters GLUT 4 and their translocation into the cell membrane (Bell et al., 1990). Then, glucose is actively transported into the cells by the transporters, molecule by molecule (Jurcovicova, 2014; Szablewski, 2017a, 2017b). In this context, insulin is the effector of an excellent signaling system directing glucose to those regions of the body, were it is required. Insulin resistance is characterized by elevated blood levels of insulin and glucose.

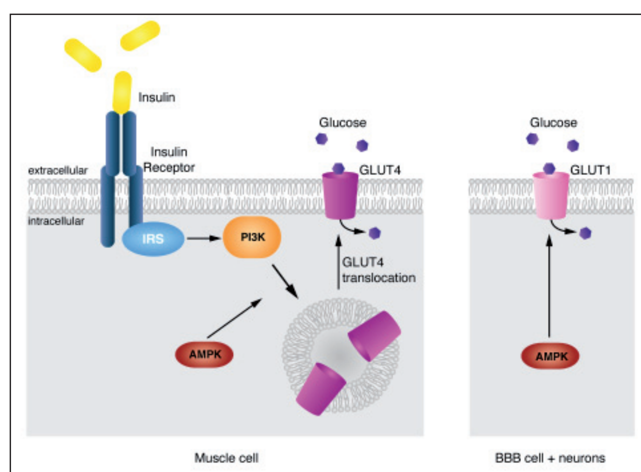

Fig. 1: IRS: Insulin receptor substrate, PI3K: Phosphoinositide 3 –kinase, AMPK: Actenosin monophosphate-activated protein kinase (adapted from Elmadhun et al. 2013)

It is suggested that in type 2 diabetes, a decrease in peripheral insulin receptor density and insufficient incorporation of GLUT4 along the mostly peripheral cell membrane results in lower cellular insulin-dependent glucose uptake and higher blood glucose levels (Garvey et al. 1998). A further pathomechanism in type 2 diabetes is the insufficient inhibition of gluconeogenesis and glycogenolysis (Magnusson et al. 1992). As a direct consequence of elevated blood glucose levels, the pancreas increases insulin secretion (hyperinsulinemia), which subsequently aggravates insulin resistance and comes along with a decrease in insulin secretion capacity (Shanik et al. 2008). Dysfunctional insulin secretion is triggered by reduced GLUT1 transporter activity of beta cells in the pancreas (Del Guerra et al. 2005). Insulin deficiency in the blood causes increased glucagon levels, which further exacerbate hyperglycemia. If disease progression is not inhibited by lifestyle modification or other measures, type 2 diabetes results in a partial and ultimately complete lack of insulin. Then, insulin therapy is required.

As outlined above, glucose is the main diagnostic parameter to diagnose type 2 diabetes, both in impending as well as manifest stages. High blood glucose is critical in any case. If untreated, it results in hyperglycemia, a potentially life-threatening condition associated with diabetes: In type 1 diabetics, hyperglycemia results in diabetic ketoacidosis, which is triggered by a lack of insulin. In contrast, hyperglycemia in type 2 diabetics is a mainly hyperosmolar condition. In type 1 diabetes, a high amount of ketone bodies is produced via ketogenesis, resulting in ketoacidosis, a highly harmful metabolic condition. In type 2 diabetics, the increased osmotic pressure induced by high glucose levels can provoke a hyperosmolar hyperglycemic syndrome that results in severe dehydration and sodium depletion as a consequence of the osmotic diuresis (De Beer et al. 2008; Umpierrez et al. 2002).

In addition, hyperglycemia exerts its negative effect by harming the vascular capillary system (Rask-Madsen and King 2013). It may also affect the tight junctions of the Blood Brain Barrier (BBB) resulting in an impairment of the BBB, leading to neuronal dysfunction (Noe et al. 2020). On the other hand, hypoglycemia is an equally serious condition. Depending on severity and duration, it potentially results in coma or death by induction of ischemia or changes in depolarization or repolarization, even leading to sudden cardiac death in selected cases (Frier et al. 2011; Kalra et al. 2013). Moreover, hypoglycemia can come along with debilitating long-term effects on cognitive functioning (Asvold et al. 2010).

Diabetes therapy is based on three pillars: (strongly carbohydrate reduced) diet, physical exercise and medication, i.e., antidiabetics – substances aiming to stabilize physiologic glucose levels, e.g., by re-activating the insulin signaling pathway (Aronoff et al. 2004). Thereby, blood glucose decreases and the cellular energy supply can be optimized (Aronoff et al. 2004; Gleizes et al. 2016; Grundy et al. 2004).

6. Glycation and inflammation

A severe consequence of high glucose levels in diabetic patients are vascular alterations due to glycation reactions. Glycation defines the non-enzymatic reaction between a carbohydrate and a protein that is not induced by the controlled enzymatic process of glycosylation, but by a simple chemical reaction between the aldehyde or keto group of a sugar and a functional group of an amino acid resulting in advanced glycation end products (AGEs) (Ulrich and Cerami 2001). Glycated hemoglobin (HbA_{1c}) has become an important diagnostic parameter in diabetes management. Microvascular events correlate with elevated HbA_{1c} levels (Demirtas et al. 2015). However, glycation is not limited to the protein hemoglobin but may affect all circulating proteins as well as vascular membranes. Permanently elevated blood sugar levels alter protein structures by glycation (Brownlee 1995), giving rise to further functional loss of endothelial cell layers (Brownlee 2001) and leading to macro- and microangiopathies (Yamagishi et al. 2017). This process is responsible for secondary complications of diabetes, such as nephropathy, neuropathy, retinopathy and cataract (Demirtas et al. 2015).

However, vascular membrane dysfunction does not exclusively depend on the action of glycation products but also on membrane fluidity. This indicates that the pathophysiologic mechanisms in non-type 1 diabetes are more complex and suggests that a therapeutic intervention exclusively aiming to reduce high glucose levels might not be sufficient in any case (Jud and Sourij 2019). According to the "membrane theory of diabetes", an impaired fluidity of endothelial cell membranes is causative for reduced efficacy of both insulin receptors and glucose transporters (i.e., GLUT4) at the cell membranes, leading both to hyperinsulinemia (Saltiel and Kahn 2001) as well as insufficient (peripheral) glucose supply. The concept links vascular dysfunction and impaired glucose transport with the reduced efficacy of insulin signaling. It connects all three secondary diseases of the metabolic syndrome directly to membranous (atherosclerotic) dysfunction (Gleizes et al. 2016; Pilon 2016; Sorci-Thomas and Thomas 2016).

Glycation is not limited to glucose but describes a fundamental reactivity of sugars. Glucose shows a relatively low glycation activity when compared to fructose (20% of fructose) (Suárez et al. 1989). The pathophysiological effect of the glycation reaction is due to the change of protein configuration induced by the covalent reaction between the sugar and the protein. The immune system mistakes the new shape of the autologous protein as a pathogen, the resulting immune response ranges from inflammation to autoimmune diseases (Graves and Kayal 2008). Inflammation induced by glycation is just one option to explain inflammatory vascular processes. As a matter of fact, inflammatory processes originate

from a disturbance of the cell membrane, which is followed by a liberation of arachidonic acid from the membrane to induce the arachidonic acid cascade with a plethora of inflammatory follow-up steps (Samuelsson 1982). Thus, whenever the steady process of formation and reformation of membranes is disturbed, an inflammatory process will be initiated. It may be assumed that this contributes to the negative effects of trans-fatty acids (Lopez-Garcia et al. 2005) that cannot be adequately metabolized after being integrated into a cell membrane due to the arrangement of their double bond. Growing evidence suggests that inflammatory changes at cell membranes slowly develop into a state called silent inflammation and that they are relevant for vascular complications in diabetes, frequently resulting in atherosclerosis (Feng et al. 2005; Libby and Aikawa 2002; Steyers and Miller 2014). Thereby, low-grade inflammation is chronically present along endothelial regions. Glycation, LDL and apolipoproteins, especially apolipoprotein B100, seem to play a major role in this process (Jenkins et al. 2004; Soran and Durrington 2011) and the induction of apolipoprotein expression in the liver triggered by fructose consumption is just one example of how LDL and apolipoprotein levels are influenced (Schaefer et al. 2009; Swarbrick et al. 2008). These inflammatory processes not only affect peripheral vessels but are highly relevant for vascular dysfunctionality in the CNS as well. This has led to the proposal to expand the concept of the metabolic syndrome by the cerebral metabolic syndrome (Noe et al. 2020).

As described above, vascular inflammation is a key element in atherosclerosis. On the other hand, inflammatory processes in central nervous regions are gaining importance among the hypotheses of neurodegeneration (Chitnis and Weiner 2017; Heneka et al. 2015). Recently, inflammation of the brain vascular endothelium, which constitutes the blood-brain-barrier, has received attention as an important step in neurodegeneration (Noe et al. 2020). In this context, the inflammation-infection-interplay leading to chronic inflammation has been extensively discussed (Noe et al. 2020).

7. Carbohydrates for sugar replacement

As already outlined, glucose is in the focus of diabetes diagnosis and therapy. Both impaired glucose tolerance and elevated glucose levels are markers for diabetes. This has led to the wrong assumption that glucose is a dangerous molecule (Aronoff et al. 2004). Sugar avoidance is a widely accepted and promoted concept in preventing obesity and diabetes. However, it is essential to differentiate between distinct types of sugar. In this context, sugar is meant to be saccharose. Saccharose is a disaccharide consisting of a glucose and a fructose molecule. In the intestines, it is cleaved quickly. Glucose is then released into the blood within about 30 min, while fructose is mainly metabolized to fat intrahepatically without influencing blood glucose levels. Carbohydrates that do not contain glucose do not directly influence the blood sugar level – unless they are metabolized to glucose – and therefore do not directly activate the insulin system. The basic concept of many anti-diabetic diets is to replace glucose, wherever feasible (Deed et al. 2015). It is not surprising that shelves of grocery stores are filled with sweeteners and sugar substitutes, mainly sugar alcohols such as mannitol, sorbitol, xylitol, maltitol, lactitol, erythritol, just to name a few. It may be an advantage that they do not activate the insulin system. They are metabolized *via* carbohydrate pathways, if required even to glucose. They usually have a considerable laxative effect (Grembecka 2015). However, an anti-obesity effect by caloric restriction can only be observed if these sugar substitutes are not fully absorbed by the intestines.

8. Sweetness and sweeteners

Glucose is best known as a physiological energy source and is linked to the sweet taste. Sweetness is detected by chemosensory receptors of the tongue, however it was shown that these receptors can also be found elsewhere in the gastrointestinal tract as well as the hypothalamus (Lee and Owyang 2017). Glucose has only 70% of the sweetening power of sucrose (beet or cane sugar) and only about 55% of that of fructose, but glucose is the most appropriate sugar to quickly improve fatigue and concentration difficulties. It is the main agonist of sweet taste receptors on the tongue. These G-protein coupled membranous receptors communicate the perception of sweetness *via* sensory afferent fibres to specific brain regions that are linked to taste perception (Lee and Owyang 2017). The activation of this pathway immediately induces insulin secretion. Prolonged presence of glucose and insulin in blood are determined by the characteristics of the kinetics of intestinal digestion of starch liberating glucose. Additionally, partial hydrolysis of starch by salivary amylases in the mouth leads to early glucose release and the perception of sweetness. This mechanism is considered to have influenced human evolution by directing nutrition towards energy rich carbohydrates, finally leading to the rise of agriculture in younger stone age (Breslin 2013). From an evolutionary standpoint, it is likely that the highly complex and tightly controlled nature of pulsatile, mostly demand-oriented insulin release confers a survival advantage to the organism (Satin et al. 2015). It remains to be clarified whether the increased frequency of pulsatile insulin secretion coming along with elevated sugar consumption is in fact a disadvantage compared to the prolonged effect induced by slowly digested food (Parada and Santos 2016).

In contrast to sugar substitutes, artificial sweeteners are calorie-free and therefore basically suited for caloric restriction. Their sweetening power is by far higher than that of sugar. There is an established list of sweeteners accepted for food production, such as saccharin, sodium cyclamate, aspartame, acesulfame, stevia and thaumatin. Due to strictly regulated approval procedures, the list of available sweeteners is growing only slowly. It has been discussed, whether artificial sweeteners potentially provoke insulin secretion by targeting relevant chemoreceptors of the tongue (Parada and Santos 2016; Wolever and Miller 1995), however, further research is needed to elucidate the effects on the insulin system. It may be assumed the related non-physiological lack of blood glucose causes craving for carbohydrates. It has been shown in animal experiments that feeding with sweeteners directly induces obesity (Mitsutomi et al. 2014) and it has been published that sweeteners can raise the incidence of dementia (Pase et al. 2017). We assume that this is rather a direct result of a constantly unmet demand for glucose, which is the brain's main source of energy, than of unknown toxic side effects of sweeteners (Lee and Owyang 2017).

9. Hunger and satiety

A comparably complex situation is given by the feeling of hunger. Signaling of sweetness is based on the interaction of a membranous receptor with the main agonist glucose and other sweet compounds. As outlined above, the hypothalamus not only responds to signals from the receptors of the tongue, but carries its own receptors for molecular glucose, just as the intestines, where digestion takes place and glucose is released from starch. Finally, pancreatic beta cells and other glucose-sensitive cells contribute to nutrient homeostasis (Schuit et al. 2001). The complex glucose receptor network is certainly not yet fully understood. The glucose system has maintained its fundamental functional role throughout evolution and has evolved into an increasingly complex functional system controlling energetic homeostasis and food intake, deserving systemic research. The hypothalamic regulation of feeding behavior involves a complex interplay of various neural and humoral signals, with leptin and ghrelin as the main regulating hormones. From the point of evolution, the sense of hunger can probably be traced back to neuronal glucose deficiency. It represents the physiological need for providing energy by eating. The feeling of satiety, on the other hand, means the absence of hunger that is initiated by food intake, resulting in the release of so-called "satiety-factors, e.g., cholecystokinin, ghrelin, glucagon-like peptide-1 or peptide YY (Ahima and Antwi 2008).

It is evident that the comparatively low quantity of about 100 grams (liver) to 400 grams (muscles) of stored glycogen should be considered a short-term back-up option in case of glucose deficiency. Gluconeogenesis, on the other hand, produces glucose by recombination of small metabolites, above all pyruvate, dihydroxyacetone and oxal-acetate. Together with glycogenolysis,

this process becomes the main source of glucose as soon as carbohydrate supply *via* nutrients is too low. In humans and all other vertebrates, amino acids from proteins are the main source for gluconeogenesis (Petersen et al. 2017). This means that in all diets low in carbohydrates, proteins and amino acids, respectively, become the source of glucose supply. The same happens during starvation when components of the body's own proteins are used for gluconeogenesis. Long-term diets might be effective in terms of weight loss but are far away from physiologically regulated energy homeostasis. In any case, the variety of glucose sources does not automatically mean that glucose is easily available whenever required – they are rather the result of evolutionary progress that was triggered by the need for a quickly available, indispensable source of energy. However, its permanent presence in the body cannot be taken for granted.

Although it is known that aging people tend to develop a strong desire for carbohydrates and sweets, this has not yet been interpreted as a potential lack of glucose in the brain. Similarly, the well-known insomnia of diabetic patients and insomnia in elderly people could both be traced back to a lack of glucose (Bendtson et al. 1992). There may still be some way to go to understand all mechanisms of nutrition and energy homeostasis, including the role of glucose concentration in the brain, but evidence suggests to take care of an appropriate availability of glucose in the brain of elderly people (Bellisle et al. 2012).

10. The energy demand of the brain

In view of the brain as the central control element for survival, its strict separation from the remaining physiological systems within the body is reasonable. This separation is ensured by a specific structure of the vascular endothelium called the BBB. The development of the BBB is initiated by astrocytes within the central nervous system, where vascular endothelial cells express intercellular adhesion molecules (claudin and occludin) that connect their lipid membranes *via* tight junctions (Weiss et al. 2009). The emerging barrier separates the brain tissue from blood. It exhibits high electric resistance and impedes peri-cellular transport into the brain. Apart from passive diffusion of lipophilic molecules, any transport into and out of the brain is mediated by transporters (Kniesel et al. 2000; Shah et al. 2012; Wolburg and Lippoldt 2002). Therefore, it is evident that an impairment of membranous fluidity coming along with a metabolic syndrome or with atherosclerosis will harm brain cells even more than peripheral ones and should be considered a highly critical phenomenon (Jurcovicova 2014; Szablewski 2017a).

The term "cerebral metabolic syndrome" has been proposed analogously to the term "metabolic syndrome" to describe the secondary consequences of a dysfunctional BBB. The cerebral metabolic syndrome is associated with an increased risk for disease and death (Dominguez and Barbagallo 2016). It is discussed as a causative factor for the onset and/or aggravation of dementia (Noe et al. 2020). A common feature of both mentioned syndromes is that they come along with hypertension and impaired glucose tolerance. However, both conditions result in a unique complex of symptoms. In the case of the metabolic syndrome, hypertension is related to threatening myocardial infarction or stroke, while impaired glucose tolerance is a signal of developing diabetes. In the case of the cerebral metabolic syndrome, in contrast, hypertension and glucose intolerance are a signal for a lack of nutrients in the brain that is accompanied by an impairment of metabolite transport function across the BBB. Unless recognized and treated adequately, both increased blood pressure and elevated blood sugar levels point towards impending neurodegeneration and dementia.

Although it is broadly assumed that the brain will take care of an adequate supply with glucose in any case, elevated blood glucose levels could be an early sign for an impairment of the transport performance of the BBB. The mere reduction of blood glucose by activation of the insulin system does not take this eventuality into account. Although blood sugar levels are high in diabetic patients, this does not correlate with an adequate or even improved supply of glucose into the brain. Despite the potential risk of reduced cerebral glucose levels, the major part of antidiabetic drugs aims to reduce blood sugar levels by activating the insulin system. This leads to increased GLUT4 activity but does not improve the situation in the brain, if GLUT1 is impaired due to membrane stiffness or another dysfunction. In such cases, a lack of energy supply within the brain could be even worsened, since – due to the forced transport of glucose into peripheral areas – the overall amount of available glucose decreases (Jones et al. 1997; Lincoln et al. 1996). In view of the needed reduction of blood glucose levels, a broad field of anti-diabetic dietetics has emerged. Almost all of them aim to replace glucose. A wide range of sugar supplements without glucose appeared on the market as dietetic products. Artificial sweeteners additionally aim to support weight loss. Not surprisingly, such products lead to lower blood sugar levels. Further, they may affect the body mass index positively and slow down the development of a metabolic syndrome (Imamura et al. 2015). However, these efforts ignore the brain's constant demand for glucose. These dietetics do not consider that elevated blood glucose levels do not automatically mean that enough glucose is available to cover the demand of the brain and ignore that such sugar levels potentially indicate glucose deficiency in neurons and other cells in the brain.

11. Activating the glucose transport into the brain

Restoration of the transport capacity along the BBB by membrane fluidity enhancement, e.g., by nutritional omega-3 fatty acids, is an approach to face this problem (Avallone et al. 2019). Activation of the GLUT1 transporter at the BBB is an even more specific option (Vannucci et al. 1997), which has recently achieved increasing attention in research. Phosphorylation of a protein is one of the most frequent pathways of protein activation. This mechanism is also used in fast activation of GLUT1 by the enzyme adenosine monophosphate-activated protein kinase (AMPK) (Abbud et al. 2000). There is substantial progress in understanding activation of GLUT1 by phosphorylation and there are different approaches to achieve this. Meanwhile, the search for GLUT1 activators has become a highly relevant topic in drug research (Winder and Hardie 1999).

Dementia has remained one of those areas, where the therapeutic standard of modern medicine is still far from effective. Alternative methods, including Traditional Chinese Medicine, are widely used to enhance memory, to prevent dementia or to delay aging (Chen and Chen 2014; Weidinger 2017; Kumar 2006). Several agents used in these alternative concepts contain components, particularly AMPK-activators, which activate GLUT1 (Ronnett et al. 2009). Most remarkably, *Ginkgo biloba*, *Panax ginseng* and many other well-known activators of AMPK and anti-aging substances are belonging to this group (Cong et al. 2011; Kim et al. 2016). It could be hypothesized that their administration not only prevents the critical rise of blood glucose levels in case of additional glucose intake, but also supports an overall reduction of blood glucose, thus securing the presence of indispensable glucose in the brain. This approach could contribute to avoiding or at least delaying the onset of insulin resistance (Ruderman et al. 2013; Winder and Hardie 1999).

Obviously, these findings and theories do not justify an immediate change in diabetes therapy. Nevertheless, enhanced activation of GLUT1 could be considered as an option in preventing some of the underlying mechanisms in diabetes pathophysiology. Therapeutic options supporting this hypothesis already exist. It is known that the oral antidiabetic drug troglitazone activates GLUT1 expression (Kausch et al. 2001). Moreover, metformin is known to be an AMPK activator (Fryer et al. 2002). Metformin has even been shown to come along with preventive properties in terms of Alzheimer's disease (Cheng et al. 2014). Interestingly, according to our knowledge, none of the hitherto reported effects of these drugs has been related to the activation of GLUT1 transporters at the BBB, although it can be assumed that this effect is at least contributing, if not decisive for their efficacy in diabetes therapy and in prevention as well as future treatment of dementia.

The proven correlation between adult-onset diabetes and dementia can be interpreted as a signal for a waning transport capacity of vascular membranes. Hypotheses that insulin-induced transport of

glucose into peripheral tissue might contribute to the development of dementia by reducing the amount of available glucose should be challenged and hopefully falsified.

12. Obesity, type 2 diabetes, and dementia

Obesity induced by nutritional misbehavior results in reduced membrane fluidity, a condition that might be linked to the rising prevalence of diabetes among young obese people supporting the membrane hypothesis of diabetes.

In view of the regulatory role of the hypothalamus in terms of cerebral glucose availability, there is a high probability that reduced availability of glucose in the brain due to a dysfunctional BBB might induce the increase of blood sugar levels. Under this aspect, high glucose levels potentially indicate insufficient glucose availability in the brain, increasing the risk for neurodegenerative processes. Neuronal apoptosis describes the pathophysiologic process that turns regular brain aging into dementia. The apoptotic process is mediated *via* intracellular cascades and starts with dysfunctional cell metabolism (Mason and Rathmell 2011). Apoptosis can be defined as the controlled dismantlement of a cell from the inside. It is usually initiated within mitochondria that control the energetic metabolism of a cell (Hengartner 2000; Martinvalet et al. 2005). With glucose being the main energy source of the brain, a permanent and adequate intracerebral availability of glucose is crucial to delay mitochondrial apoptotic processes. A lack of glucose has been directly associated with neuronal cell death and apoptosis (Ouyang et al. 2000).

13. Solving the sugar dilemma

The focus on the impairment of the BBB plays a central role in the development of treatment options of the cerebral metabolic syndrome and subsequent conditions. Within this concept, the etiology of dementia is rather based on metabolic than on direct genetic factors. Cerebral glucose and nutrient deficiency weaken neuronal metabolism and provoke disease progression. Just like in the metabolic syndrome, preventive measures are of special importance to hold back pathological processes at the beginning of the disorder. The most important step in this scenario is an appropriate supply of the main energy source in the brain, glucose. Especially elderly people and patients suffering from diabetes should be aware of that. Activation of GLUT1 at the BBB may provide an approach to overcome this challenging dilemma. It may be expected that activation of GLUT1 contributes to a reduction of blood glucose levels and, at the same time, secures glucose supply to the brain, thus preventing apoptotic and other detrimental processes induced by cerebral hypoglycemia. The dysfunction of the BBB provides a rational approach for preventive measures in neurodegenerative diseases, which goes even beyond glucose transport and affects also other nutrients and metabolites.

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