PUBLICACIÓN CONTINUA

The Randle cycle, the precarious link
between sugars and fats

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ABSTRACT

Obesity is a growing global health concern, closely related to cardiovascular diseases. Understanding the correlation between excessive sugar consumption and the formation of fat deposits, described in the Randle cycle, will allow us to have a better grasp on metabolic processes that disrupt the balance between fat formation and degradation processes. The goal of this review is to expand and update the information about the Randle cycle and describe their different levels of regulation. In addition, the participation of mTORC1 and the AMP dependent Kinase (AMPK) during the postprandial and fasting states is described.
Keywords: metabolic syndrome, hepatotoxicity, fructose, lipogenesis, mTORC1, AMPK, dyslipidemia, Randle cycle.

El ciclo de Randle, el precario vínculo entre azúcares y grasas

RESUMEN

La obesidad es un problema de salud global, asociada con enfermedades cardiovasculares. El análisis de la relación existente entre el elevado consumo de glucosa y la concomitante formación de depósitos de grasa, descrita por el ciclo de Randle, permitirá desarrollar una comprensión de los procesos metabólicos involucrados en el balance entre la formación y la degradación de los lípidos. Esta revisión tiene como objetivo**,** proporcionar una actualización del ciclo y de sus diferentes niveles de regulación, así como la participación de mTORC1 y la cinasa dependiente de AMP (AMPK) durante el estado postprandial y de ayuno.
Palabras clave: síndrome metabólico, hepatotoxicidad, fructosa, lipogénesis, mTORC1, AMPK, dislipidemia, ciclo de Randle.

INTRODUCTION

*I*n accordance with data from the World Health Organization (WHO), diseases associated with obesity have become one of the main health problems worldwide. The number of overweight people in almost every region of the world (except in certain sub-Saharan African regions and some Asian areas) has been increasing at a constant annual rate of 0.7% since 1975 to the end of the second decade of the 21st century (World Health Organization, 2018) Using the body mass index (BMI) scale, the WHO pointed out that in 2016, more than 39% of people older than 18 years old (more than 1,900 million) were overweight, while 13% of the world's population (more than 650 million people) was diagnosed with obesity. Among children and teenagers within the age interval of 5-19 years and children under 5 years old, 18% (over 340 million) and 6% (more than 113 million children) were overweight, respectively (Murray, 2019; Pearlman, Obert & Casey, 2017; Stanhope, 2016). This worldwide phenomenon in which there are more overweight than underweight people was recognized since the last third of the 20th century, indicating that two out of the three countries in North America (namely, México and the United States), and many countries of the European Union, had the most affected population by this health crisis (Hruby & Hu, 2015; Ogden, Yanovski, Carroll & Flegal, 2007; Pereira *et al.*, 2020; Smith & Smith, 2016).

It is generally stated that the main cause of obesity is related to an imbalance between the calories consumed and the calories expended. In accordance with WHO experts (World Health Organization, 2018), obesity problems can be explained considering that *"there is an increased intake of energy-dense foods that are high in fat, along with an increase in physical inactivity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization"*.

However, to prevent and treat the obesity problem, experts need to clearly understand lipogenesis and lipolysis, as well as the processes that determine the formation of adipose tissue derived from both sugar-rich foods, whose main ingredient is fructose, and foods high in fat (Moran & Ladenheim, 2016; Priyadarshini & Anuradha, 2017). In other words, it is essential to understand the glucose-fatty acid cycle, also known as the Randle cycle, to recognize the causes of obesity and propose preventive and effective measures (Randle, Garland, Hales & Newsholme, 1963).

Likewise, the general population should be aware of the seventy different names given to sugar that are included in processed foods, in order to keep track of excessive carbohydrate consumption (Gómez Candela & Palma Milla, 2013; Rodríguez Delgado, 2017). It is estimated that sugar-sweetened beverages (soft drinks, juices, nectars, teas, energy drinks, yogurts, among others) are the main sources of sugar in the diet, accounting for more than 15% of the daily caloric intake. Besides, many people do not even realize that their consumption of sugar-sweetened beverages and low-nutrient density foods is much more frequent than they think (Jensen *et al.*, 2018; Rodríguez Delgado, 2017).

This increase in sugar consumption has been associated with pathologies such as liver steatosis, type 2 diabetes mellitus, simple and combined hyperlipidemias (hypertriglyceridemia and hypercholesterolemia), cardiovascular diseases (hypertension, and heart failure) and dental caries, the latter originally described as the only disorder due to sugar consumption. Therefore, in this review we updated the information regarding the Randle cycle, proposed in 1963 (Randle *et al.*, 1963), and the balance between the formation of acylglycerols and their breakdown (lipogenesis/lipolysis).

THE RANDLE CYCLE AND ITS ASSOCIATION WITH THE BALANCE BETWEEN LIPOGENESIS AND LIPOLYSIS
Postprandial state

Under hyperglycemic conditions, such as the postprandial state, insulin induces an increase in the expression of glycolytic regulatory enzymes (glucokinase; phosphofructokinase 1, PFK-1; and pyruvate kinase) and the glucose transporter GLUT 4 (Figure 1). Insulin also activates genes that code for enzymes involved in the Randle cycle (Table I), leading to an increase in the glycolytic and Krebs cycle fluxes and the stimulation of anabolic pathways, such as lipogenesis, β-reduction [synthesis of fatty acids in the cytosol catalyzed by the Fatty Acid Synthase (FAS)], phospholipogenesis and cholesterogenesis (Marcelino *et al.*, 2013; Nakamura, Yudell & Loor, 2014; Palomer, Salvado, Barroso & Vázquez-Carrera, 2013; Possik, Madiraju & Prentki, 2017).

In terms of metabolic pathways, it can be inferred that a sugar overload in glycolysis will drive some of the glucose carbons towards dihydroxyacetone phosphate (DHAP) (Figure 1), which is involved in the formation of acylglycerols (lipogenesis) and phospholipids (phospholipogenesis) (Song, Xiaoli & Yang, 2018) (Figure 1). Therefore, glycolytic flux and anaplerotic pathways are activated in the presence of insulin (Ameer, Scandiuzzi, Hasnain, Kalbacher, & Zaidi, 2014; Bartelt *et al.*, 2013; Summermatter *et al.*, 2009).

Carbon overload in glycolysis is also associated with the transfer of citrate from mitochondria to the cytosol, where oxaloacetate (OAA) and acetyl-CoA are produced by the ATP citrate lyase (Figure 1). The first of these metabolites can be reduced or transaminated and returned to the mitochondrial matrix, forming part of the malate-aspartate shuttle.

Figure 1. Metabolic pathways involved in the extended Randle cycle. Abbreviations: GK: Glucokinase; PFK-1: Phosphofructokinase-1; PK: Pyruvate Kinase; PDC: Pyruvate Dehydrogenase Complex; PEPCK: Phosphoenolpyruvate Carboxykinase; PCmt: mitochondrial Pyruvate Carboxylase; ACC: Acetyl-CoA Carboxylase; HMGCoA reductase: Hydroxymethylglutaryl-CoA reductase; acyl-ACP: acyl-acyl-carrier protein; LPL: Lipoprotein Lipase; HSL: Hormone-Sensitive Lipase; CAT1: Carnitine Acyltransferase 1; Chol: Cholesterol; TAG: Triacylglycerol; DAG: Diacylglycerol; FABP: Fatty Acid Binding Protein; FATP: Fatty Acid Transporter Protein; FAT/CD36: Fatty Acid Transporter. Enzymes and pathways stimulated by insulin are highlighted in black; enzymes and pathways activated by glucagon and norepinephrine are highlighted in blue. Black boxes without color frames indicate enzymes whose overexpression increases in the postprandial state; blue boxes indicate enzymes up-regulated by fasting (glucagon and epinephrine). Black boxes with yellow frames indicate the main pathways promoted in the postprandial state. Blue boxes with a green frame highlight the main pathways activated during hypoglycemia resulting from fasting. * Reactions that take place in the mitochondrial matrix. Modified from Nelson & Cox, 2017; Aguilar *et al.* 2017.

Acetyl-CoA can take two pathways in the cytosol: the formation of fatty acids or the synthesis of cholesterol (Figure 1). Fatty acid formation is controlled by the FAS and the presence of allosteric regulators of the acetyl-CoA carboxylase (ACC) (Figure 1). In the presence of insulin, β-oxidation (the mitochondrial catabolic process of breaking down fatty acids) is inhibited by malonyl-CoA, stopping the transport of fatty acids into the mitochondrial matrix mediated by the fatty acid transporter Carnitine Acyltransferase 1 (CAT1) (Figure 1).

Regarding cholesterol formation, the pathway is regulated by the hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase). The fate of acetyl-CoA's carbons can be defined as

tissue-dependent, and regulated by the formation of malonyl-CoA and mevalonate metabolites, which control the rate of β-reduction and cholesterogenesis, respectively (Barbosa & Siniossoglou, 2017; Kory, Farese Jr. & Walther, 2016; Mottillo *et al.*, 2014; Rambold, Cohen & Lippincott-Schwartz, 2015).

Insulin also increases the expression of lipoprotein lipase (LPL) in the postprandial state. This allows the hydrolysis of plasma triacylglycerol (TAG) from exogenous sources (diet), found in chylomicrons, and endogenous sources (hepatic), present in the Very Low Density Lipoproteins (VLDL) (Figure 1). Proper LPL functioning is associated with adapter proteins that stabilize and activate LPL (Quiroga & Lehner,

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Table I. Enzymes involved in the Randle cycle. Insulin increases the entry of glucose into the cells, the rate of glycolysis, the pentose phosphate pathway, as well as some anabolic pathways that are fed by the carbon skeletons derived from glucose. Some examples concerning these pathways are β-reduction and lipogenesis. Modified from Nelson & Cox, 2017.

Increased expression	Metabolic pathway
Hexokinase II	Glycolysis
Hexokinase IV	Glycolysis
Phosphofructokinase-1	Glycolysis
Pyruvate kinase	Glycolysis
Phosphofructokinase-2/ Fructose-2,6-bisphosphatase	Glycolysis/gluconeogenesis regulation
Glucose 6-phosphate dehydrogenase	Phosphopentose pathway
6-phosphogluconate dehydrogenase	Phosphopentose pathway
Pyruvate dehydrogenase complex	Krebs cycle entry
Acetil-CoA carboxylase	β-reduction
Malic enzyme	β-reduction
Citrate lyase cytosolic	β-reduction
Fatty acid synthase	β-reduction
Acyl-CoA-glycerol transferase	Lipogenesis
Decreased expression	**Metabolic pathway**
Phosphoenolpyruvate carboxykinase	Gluconeogenesis
Glucose 6-phosphatase	Glycemic regulation

2012), such as apoprotein C-II on the smooth and skeletal muscles, and adipose tissue (Figure 1). Also, hydrolysis of TAG is more efficient when apoprotein C-V is active.

Fasting conditions
Under fasting or starvation conditions, lipolysis in white adipocytes is increased by hormones, such as glucagon (Pereira *et al.*, 2020) and norepinephrine, which activate the hormone-sensitive lipase (Figure 1), and decrease the activity of the enzymes that control lipid anabolism, such as HMG-CoA reductase, ACC, and LPL (Hilton, Karpe & Pinnick, 2015; Quiroga & Lehner, 2018; Rambold *et al.*, 2015). Due to their hydrophobic character, free fatty acids exported to the blood plasma are transported by albumin toward the muscle and liver tissues. Uptake of fatty acids into the liver or muscle cells is carried out by Fatty Acid Binding Protein (FABP), Fatty Acid Transporter Protein (FATP), and Fatty Acid Transporter (FAT-CD36) (Figure 1). Intracellular fatty acids are then activated in the form of acyl-CoA in hepatocytes

and muscle cells and subsequently translocated into the mitochondrial matrix by the fatty acid transporter CAT1 and degraded by β-oxidation (Figure 1).

Acetyl-CoA overproduction by β-oxidation of fatty acids causes the allosteric inhibition of the pyruvate dehydrogenase complex (Figure 1). This allows the production of OAA from pyruvate, and thus the beginning of hepatic gluconeogenesis (Figure 1) (Fuchs *et al.*, 2012; Sánchez-Gurmaches *et al.*, 2018). Glycerol obtained from TAG degradation is incorporated at the level of DHAP, feeding the gluconeogenesis in the liver (Figure 1). Glycerol is the most efficient gluconeogenic substrate, compared to alanine, lactate, and other carbon skeletons of some gluconeogenic amino acids (Figure 1). In energy terms, the synthesis of one molecule of glucose from glycerol requires two ATP molecules, instead of six ATP equivalents if gluconeogenesis begins from pyruvate (Fry & Carter, 2019; Pietrocola *et al.*, 2017).

HEPATIC METABOLISM OF FRUCTOSE
Fructose, obtained from fruits and honey, is an intense-flavor sweetener that is added to most processed foods (Bray, 2013; Feinman & Fine, 2013). Fructose presentations include free fructose, sucrose, polysaccharides (fructans) in syrups and nectars, among others (Choo *et al.*, 2018). The rise in fructose consumption has been associated with the increase in obesity and the onset of the metabolic syndrome (Elliott, Keim, Stern, Teff & Havel, 2002; Sievenpiper *et al.*, 2014) (Figure 2). This type of sugar is metabolized largely by hepatocytes, and its assimilation takes place in parallel with the catabolism of other hexoses in glycolysis (Ter Horst & Serlie, 2017). Glut 2 mediates the transport of fructose into the hepatocytes, and the monosaccharide is phosphorylated by fructokinase C, also known as ketohexokinase. Glyceraldehyde and DHAP are produced from fructose 1-phosphate by aldolase B, which allows the integration of fructose into the middle part of glycolysis (Figure 2).

Fructose is a highly lipogenic sugar in comparison with other monosaccharides (Loza-Medrano *et al.*, 2019; Mai & Yan, 2019), because it enters the glycolytic pathway without any allosteric or hormonal control of the fructokinase C. For instance, hexokinases and PFK-1 prevent an accelerated rate of ATP consumption and avoid the overproduction of ADP and trioses that feed lipogenesis (Abdelmalek *et al.*, 2012; Mock, Lateef, Benedito & Tou, 2017).

The increase in the formation of DHAP derived from fructose metabolism, augments the synthesis of fatty acids and the accumulation of triacylglycerol deposits that can progress to steatosis (Figure 2), along with an increase in VLDL and a decrease in High-Density Lipoproteins (HDL) (Ishimoto *et al.*, 2013; Roglans *et al.*, 2007).
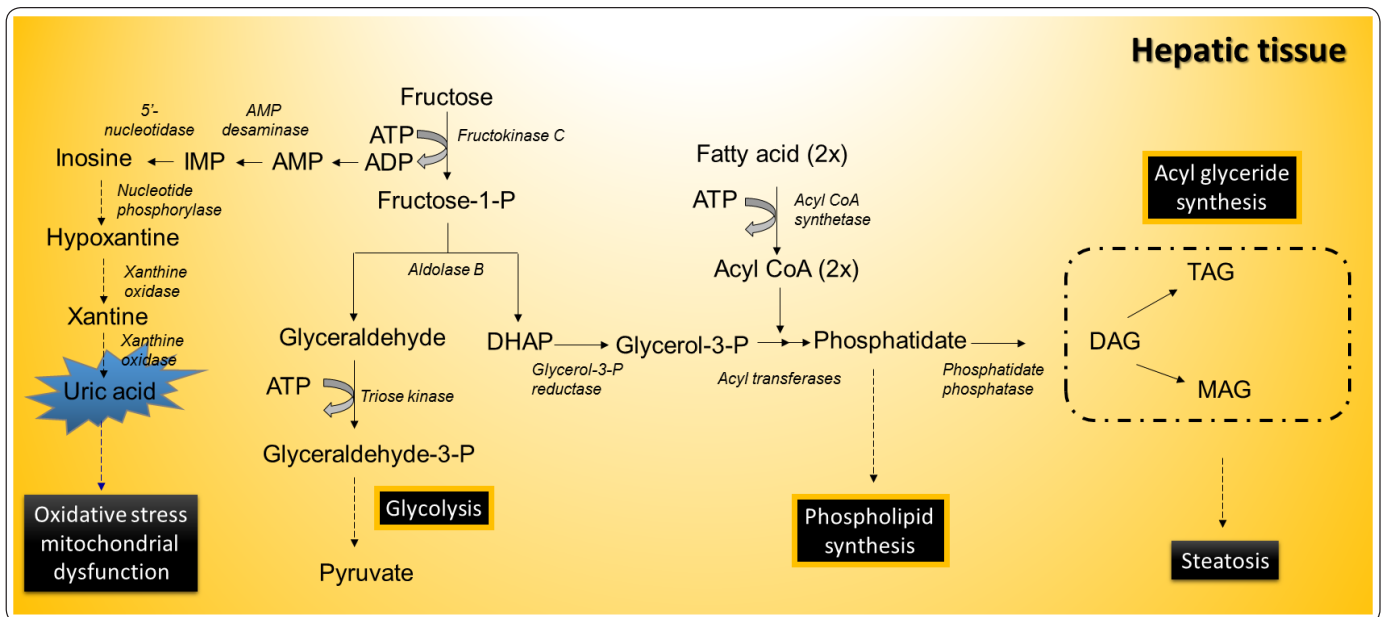
Figure 2. Metabolic pathways involved in the assimilation of fructose. Abbreviations: TAG, Triacylglycerol; DAG, Diacylglycerol; MAG, Monoacylglycerol; IMP; Inosine monophosphate; AMP; Adenosine monophosphate. Modified from Nelson & Cox, 2017.

At the molecular level, frequent fructose intake increases the production of mRNAs for FAS and the stearoyl-CoA desaturase 1 (SCD1), which stimulates the synthesis of triacylglycerols and the introduction of the first double bond to the saturated fatty acids, respectively (Basaranoglu, Basaranoglu, Sabuncu & Senturk, 2013). In addition, fructose increases the mRNA of the Carbohydrate-Responsive Element-Binding Proteins (ChREBP) and the mRNA of proteins that participate in the STAT3 pathway involved in the release of leptin (Roglans *et al.*, 2007). It has been stated that ChREBP is a transcription factor that regulates the synthesis of enzymes participating in glycolysis, fructolysis and gluconeogenesis. Also, ChREBP is involved in the *de novo* synthesis of triacylglycerols and cholesterol, regardless of insulin activation (Ter Horst & Serlie, 2017).

Frequent fructose intake is associated with hypertension, insulin resistance, steatosis and hypertriglyceridemia, and causes non-alcoholic fatty liver disease in people with obesity, in which the nuclear receptor PPARαγ and its target NF-κβ participate in the decrease of the rate of β-oxidation under gluconeogenesis conditions (Costa Gil & Spinedi, 2017; Laughlin *et al.*, 2014; Roglans *et al.*, 2002). High fructose intake is also related to the onset of gout disease (Figure 1). As a consequence of the increase in fructokinase C activity and the associated high rate of ATP consumption, there is a rise in the concentrations of ADP and AMP that causes a higher production of uric acid and inflammation of some joints (Mai & Yan, 2019). The link between fructose

intake and gout arthritis has been observed in various animal models within minutes after the ingestion of fructose (Jensen *et al.*, 2018).

In addition, the increase of uric acid levels results in the activation of cytosolic NADPH oxidase that translocates to the mitochondria, generating oxidative stress and the inhibition of the aconitase 2, and resulting in the accumulation of citrate in the mitochondrial matrix (Jamnik *et al.*, 2016; Jensen *et al.*, 2018). This causes the export of citrate to the cytoplasm and the stimulation of lipogenesis and cholesterogenesis (Figure 1). The oxidative stress in mitochondria spreads to the endoplasmic reticulum, activating the Sterol Regulatory Element-Binding transcription factor 1 (SREBP-1), which in turn increases the transcript levels of genes involved in lipogenesis and cholesterol synthesis (Jensen *et al.*, 2018; Lustig, 2010; Samuel, 2011) (Figure 1).

Control of Randle cycle by mTORC1 and AMPK

The mammalian target of rapamycin (mTOR) is a kinase that forms two complexes in mammals: mTORC1 and mTORC2. mTORC1 is activated by amino acids (Chen, Wei, Liu & Guan, 2014; Cheng & Saltiel, 2006), growth factors and hormones, such as insulin (Baena *et al.*, 2015; Verges, 2018). mTORC2 is also regulated by growth factors and is involved in cytoskeleton remodeling and sphingolipid synthesis (Figure 3). During the postprandial state, insulin stimulates phosphoinositide-dependent kinase 1 (PDK1),
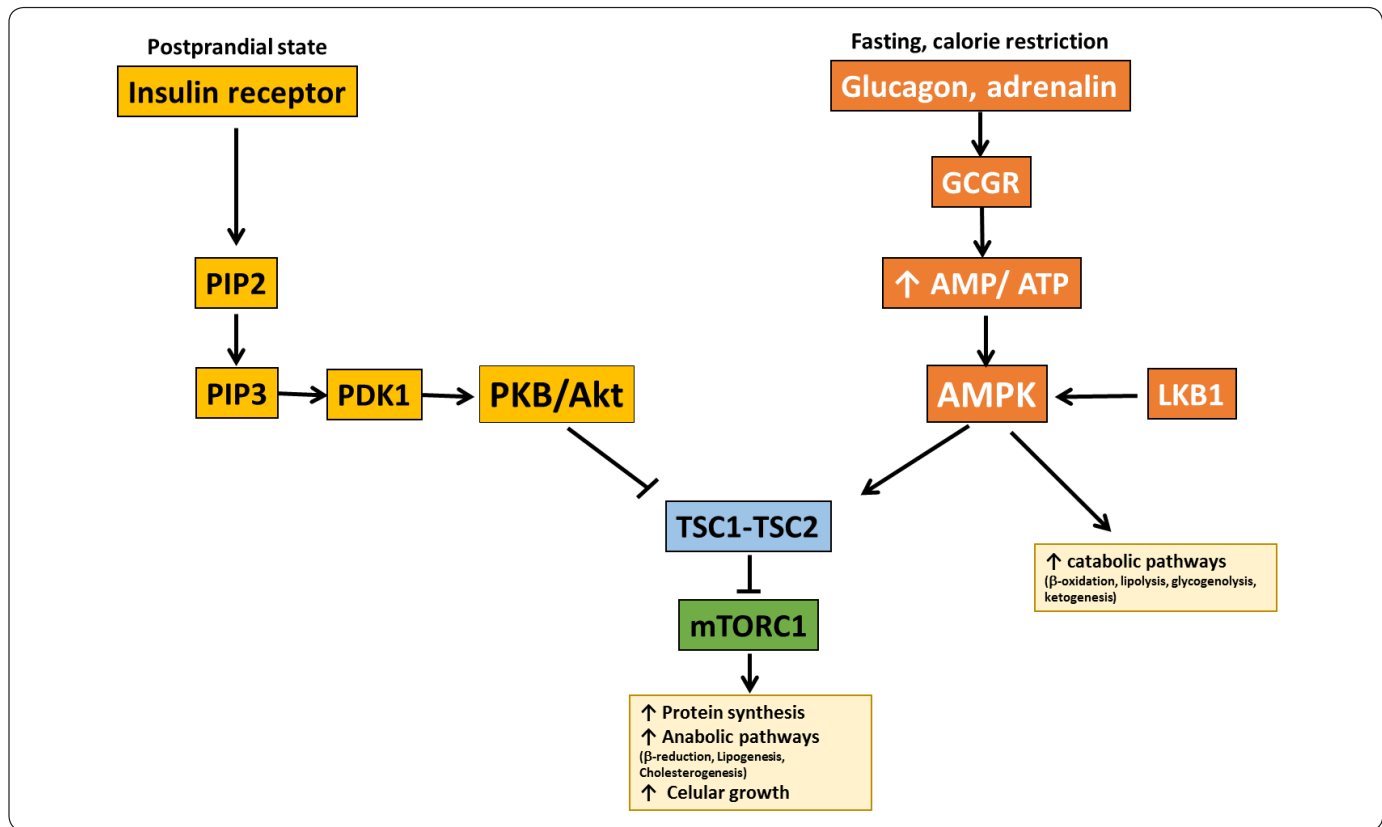
Figure 3. Functional relationships between mTORC1 and the AMP activated protein kinase (AMPK) in the Randle cycle. Abbreviations: AMPK: AMP-Activated Protein Kinase; mTORC1: mammalian Target of Rapamycin Complex 1; PIP2: phosphatidylinositol (4,5)-bisphosphate; PI3K: phosphoinositide 3 kinase; PIP3: phosphatidylinositol (3,4,5)-trisphosphate; PDK1: 3-phosphoinositide-dependent kinase-1; PKB/Akt: protein kinase B/Akt; TSC1-TSC2: 1-2 tuberous sclerosis complex (or hamartin-tuberin complex); PKA: Protein Kinase A; LKB1: Liver Kinase B1. Modified from Yoon, 2017.

which leads to the activation of PKB/Akt signaling pathway, inhibition of the TSC1/TSC2 complex (tuberous sclerosis complex 1 and 2), and activation of mTORC1, which promotes lipogenesis, glycolysis, and glycogen synthesis (Asati, Mahapatra & Bharti, 2016; Jiang *et al.*, 2008; Kumar *et al.*, 2010; Naito, Kuma & Mizushima, 2013; Verges, 2018). On the contrary, the AMP-dependent Kinase (AMPK) is hormonally downregulated under the hyperglycemia status and activated during fasting or exercise conditions. Activation of the AMPK depends on the stimulation of both the AMPc-dependent protein kinase (PKA) and the human tumor suppressor liver kinase 1 (LKB1), and the increase in the concentration of AMP (Kim & He, 2013). Along with the stimulation of PKA and AMPK there is a decrease in the main lipogenic pathways, such as fatty acid synthesis, triacylglycerol accumulation and cholesterogenesis, and activation of gluconeogenesis (Hasenour *et al.*, 2017), glycogen degradation, lipolysis and mitochondrial β-oxidation, thereby increasing ketogenesis in the liver (Cardaci, Filomeni, & Ciriolo, 2012). AMPK, through the phosphorylation of ACC and HMG-CoA reductase, inhibits the synthesis of fatty acids and cholesterol, respectively.

In short, triacylglycerol accumulation in white fat deposits, liver tissue, and between fiber bundles is caused by hypercaloric diets rich in fast-digesting carbohydrates, along with the sedentary lifestyle habits of Western societies (Perera & Turner, 2016). Hypertriglyceridemia and hypercholesterolemia are involved in the pathophysiology of health problems, such as high blood pressure, diabetes mellitus 2, atherosclerosis and obesity, among other diseases (Ke, Xu, Li, Luo & Huang, 2018; Nakamura *et al.*, 2014; Palomer *et al.*, 2013; Possik *et al.*, 2017).

Conclusions

There is a metabolic relationship between sugar consumption and fat accumulation. In the specific case of fructose, the excessive consumption of this sugar causes depletion of cellular ATP, steatosis, obesity, metabolic syndrome, and an increase in the production of uric acid. These adverse metabolic effects

are the consequence of the lack of regulatory mechanisms for the incorporation of fructose into the glycolytic pathway. A new addition to the Randle cycle is the incorporation of mTORC1 and the antagonistic effect of the AMPK to ensure an efficient regulation of lipogenesis and lipolysis, respectively. In terms of public policy, authorities of health institutes should advise against the abuse of carbohydrate consumption.

Conflicting inerests
The authors declare that there is no conflict of interest.

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