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Correlation and enlightenment between type 2 diabetes and aging from the perspective of oxidative stress

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Abstract. Type 2 diabetes is a very common type in diabetes, which is also called noninsulin-dependent diabetes. This paper focuses on the correlation between type 2 diabetes (T2D) and aging from the perspective of oxidative stress (OS), including the pathway that T2D produces oxidative stress and the effect that oxidative stress imposes on T2D. This paper also mentioned some specific mechanisms, like a glycolytic pathway, enhanced formation of advanced glycation end products (AGE), activation of protein kinase C (PKC), and deactivation of the insulin signaling pathway. In addition, this paper also talks about the important influence of OS in the process of aging. And, the attention was focused on the excessive ROS produced by mitochondria. On this basis, this paper sorts out the correlation between aging and T2D in OS and finds some experimental evidence, through which this paper also offers some enlightenment from the way of anti-aging to anti-diabetes.

Keywords: type 2 diabetes, aging, oxidative stress (OS), metformin.

1. Introduction

Diabetes, a very common metabolic disease, is characterized by hyperglycemia. The morbidity of diabetes all over the world is rapidly increasing, which has aroused extensive attention and research on it. Among them, the research on type 2 diabetes has made great progress, because it is the most common form of the disease that causes the defect in the production of insulin [1]. Recently, a great number of studies have found that type 2 diabetes is strongly associated with aging, which is a very hot research area. Their connection between them is not only intimate but also very extensive, covering almost the whole body. Some recent studies show that type 2 diabetes can affect the aging of the brain, skeletal muscle, body composition, and so on. At the same time, aging can also make changes in body compositions, like fat distribution, in adults and may contribute to the increased risk of T2D [2-4]. Even though there is no exact mechanism of T2D and aging, many studies show their positive correlation. This paper mainly reviews the relationship between T2D and aging from the perspective of oxidative stress, which is an imbalance of oxidants (like ROS) and antioxidants. Finally, this review offers the enlightenment to treat aging from the association.

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2. Mechanisms of oxidative stress in T2D and aging

2.1. Oxidative stress diabetes

Oxidative stress can develop in diabetes in several ways. The molecular mechanism of OS production in diabetes has been proved clearly, as the Figure 1 shows, and these studies point out that the central to diabetes-associated oxidative stress is the accumulation of glyceraldehyde-3-phosphate, and the molecular pathway of OS is mainly relevant to the metabolism of glucose and lipid [5]. Among the several pathways, including glycolytic pathway, enhanced formation of advanced glycation end products (AGE), activation of protein kinase C (PKC), hexosamine pathway, polyol pathway, and deactivation of the insulin signaling pathway.

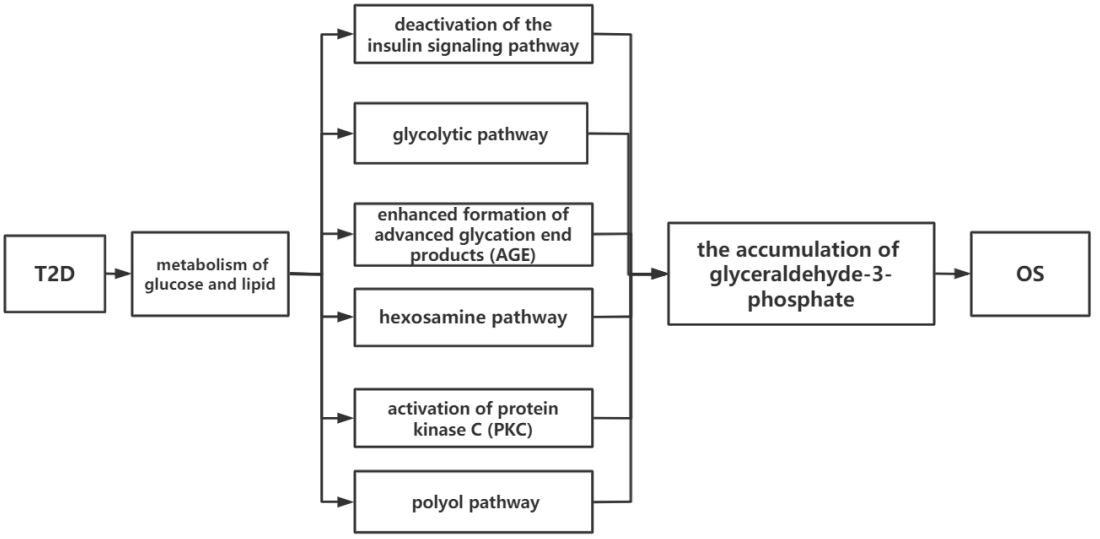

Figure 1. The mainly molecular pathway cause OS in T2D.

When focusing on the glycolysis reactions, as the Figure 2 shows, the writer claimed that under hyperglycemia caused by diabetes, the excessive ROS from glycolysis reactions can contribute to DNA damage and activation, poly-ADP-ribose polymerase 1 (PARP1) is a kind of DNA repair enzyme, which can inhibit the activity of glyceraldehyde-3-phosphate dehydrogenase and cause the accumulation of GA3P. An increase in GA3P can cause oxidative stress by inducing the autooxidation of glucose to produce hydrogen peroxide [6].

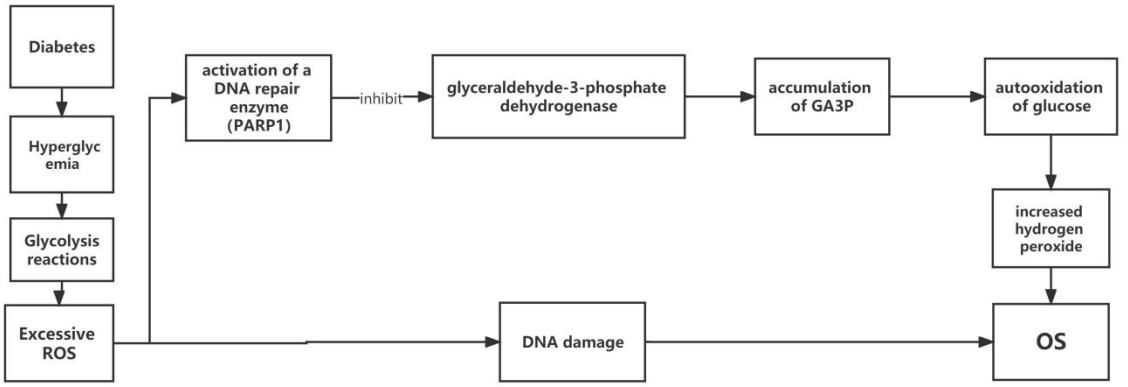

Figure 2. The glycolysis reactions pathway in T2D causes OS.

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OS is also a key component in the development of diabetes and its complications. The main features of type w diabetes are IR (insulin resistance) and deficient insulin function. There is research showing that OS is damage the β-cell. Because the excessive ROS accumulation in B-cell can damage the morphology and function of mitochondria. In turn, it causes a decrease in the quality and quantity of insulin secreted by β cells and leads to insulin resistance. Some studies claim that the excessive production of mitochondrial superoxide caused by the abnormal metabolism of diabetes is central to diabetic tissue damage [7, 8]. Not only that, but oxidative stress in the body may also cause ROS level increase due to the variation in the destruction of catalase, superoxide dismutase, and glutathione peroxidase antioxidants. Those changes may further contribute to the development of diabetic syndrome [9].

2.2. Oxidative stress in aging

Aging is a biological process with progressive deterioration in physiological functions and metabolic processes. Although people cannot find out the mechanism of aging at present, most studies point out that it is related to the excessive accumulation of ROS in mitochondria, based on the fact that mitochondria is the primary sites of reactive oxygen species production [10]. On the basis of the mitochondrial free radical theory, the theory of the mitochondrial rate of reactive oxygen species (mitROS) production is correlated with species longevity in the true sense [11]. This paper will briefly describe its mechanism. One of the definitions of OS points out that OS can be described as the superfluous amount of ROS, due to the imbalance between generation and destruction. In the main, OS can be defined as the state that characterizes ROS accumulation. The formation of excessive ROS can lead to oxidative stress, further damaging the DNA, protein, lipid, and cells [1, 12].

2.3. The correlation between type 2 diabetes and aging in oxidative stress

As this paper mentioned above, diabetes and aging can be related to oxidative stress. On the one hand, with the increase of age, the prevalence of type 2 diabetes and the glucose intolerance level both increase [1]. In that case, researchers can think of oxidative stress as one of the ways to connect them. when the body gets old, the accumulation of ROS in mitochondria will contribute to destroying the β-cell, induce IR and make other ways that may cause type 2 diabetes. Here are some data to support this consequence. T2D is related to the aging of the brain, muscle, adipose tissue, and so on. For example, inordinate absence of skeletal muscle and trunk fat mass in elder people with diabetes. Elder adults with T2D showed extravagant reductions in appendiceal lean weight and trunk fat weight in relation to subjects without diabetes. Elder women who have T2D were at particularly high-risk for decline of skeletal muscle weight, with thigh muscle lose twice as fast as non-diabetic women [13]. Studies by Lenore J. Launer have pointed out that diabetes as well as its complications are the causes of brain aging in the elderly and may lead to cognitive impairment [3].

On the other hand, patients with type 2 diabetes will also suffer from oxidative stress caused by the excessive accumulation of glycolytic-3-phosphate produced by glycolysis and other pathways, and the disproportion between oxidants and antioxidants caused by this oxidative stress will eventually accelerate the aging of the body. Here is also some data from research to support the conclusion. There is a study pointed out that the prevalence and incidence of impaired glucose tolerance (IGT) and T2D in the elderly are higher than those in the young, which may be due to factors such as insulin secretion defects related to aging, which makes the liver less sensitive to insulin with age [14]. Although we do not have a clear understanding of the mechanism of their association, we may wish to take oxidative stress as one of the entry points to find the specific pathways that link them.

2.4. Enlightenment of anti-aging from anti-diabetes drugs

T2D accounts for a large proportion of elderly patients and will continue to increase in the future, and most of them present with comorbidities [15]. Some research shows, there are a lot of conditions that associated with aging and diabetes, like osteoporosis, peripheral vascular disease and atherosclerosis [16]. All those conditions are very common in the life of elder people or patients with type 2 diabetes.

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If doctors ignore the internal relationship between those disease and aging and T2D, They most likely induce each other, aggravate the condition or cause new disease.Therefore, There is a need to link the treatment of diabetes and aging, especially in the aspect of oxidative stress. Besides, researchers already get hang of lots of the ways and drugs to treat T2D, from which we can gain enlightenment to anti-aging. Actually, some researches has proved that almost every methods using antioxidants,whether natural or synthetic, can ameliorate the complications of diabetes, and the utilize of antioxidants plays a key role in diabetes prevention [17]. When we look at anti-diabetes drugs, metformin is suitable for the mechanism. According to reports, metformin, as the most widely used antidiabetic drug, can delay aging through key landmark events affecting aging, including nutritional perception imbalance, protein balance loss, mitochondrial dysfunction, telomere wear, epigenetic changes, and cell aging, and show a protective effect on slowing down the progress of various aging-related diseases [18]. Some researchers have come to the conclusion from the data of animals such as nematodes and mice that metformin can indirectly play a beneficial role in aging and healthy life. Through its influence on cell metabolism, it can resist hyperglycemia, enhance insulin sensitivity, reduce oxidative stress, and protect endothelial and vascular functions [19]. According to the new research, metformin can get into the cell through the organic cationic transporter 1 (OCT1). And then it can delay senility by three key ways, metabolic, oxidative and inflammatory, as the Figure3 shows. Among them, the viewpoints discussed in this paper are more in line with the following functions: (1) Metformin can inhibit mitochondrial complex I and thereby oxidative phosphorylation. (2) Extracellularly, metformin is able to downregulat Insulin/IGF1 signaling. (3) The inhibition of mitochondrial also leads to AMPK-independent effects (red in the Figure 3.), especially reducing ROS, advanced glycation end-products (AGEs) and macromolecular damage [20]. These functions of metformin are in line with our previous discussion on the correlation mechanism between diabetes and aging, proving that metformin can be used to delay aging as a drug against diabetes, and also confirm our enlightenment that from antidiabetic drugs to treat aging.

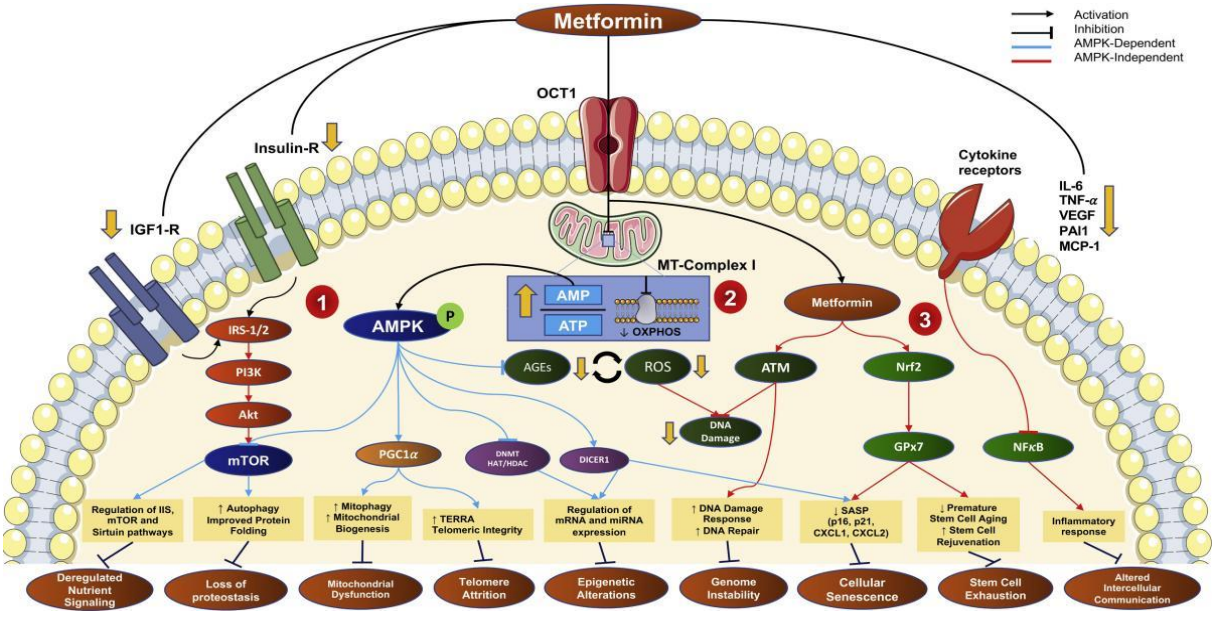

Figure 3. Mechanism of metformin in delaying aging.

After entering cells through OCT1, metformin mainly acts through three pathways: metabolism, oxidation, and inflammation. (1) Metformin can inhibit oxidative phosphorylation through mitochondrial complex I, resulting in the increase the ratio of AMP adn ATP and stimulation of AMPK. And the AMPK-related mechanisms (shown in blue) favor inhibition of the activation of mTORC1, PGC-1a, and transcriptional regulation by DNA, histone modifications, and miRNAs. (2) Restraint of mitochondrial ETC result in non-AMPK effects (shown in red), like decreased reactive oxygen species and decreased AGEs, thus reducing damage caused by macromolecular. (3) Theanti-inflammatory and

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senotherapeutic effect that independent from AMPK (show in red) of the metformin is through the down-regulation of pro-inflammatory cytokines, the NF-kB signaling pathway, and the activation of Nrf2-Gpx7 and ATM signaling pathways, respectively. All these effects weaken the aging characteristics by reducing the cell imbalance caused by aging.

3. Conclusion

As has been mentioned above, OS plays a great role in both T2D and diabetes and may be one of the vital factors that make them strongly related. So in this case, when you treat or prevent one, you can not ignore the other. And oxidative stress is a very good starting point to carry out the research in this direction. For example, if you can decrease the content of ROS in the body, you can theoretically treat both of them. Besides, this paper also agrees with gaining some enlightenment in anti-aging from the drug people use to antidiabetic drugs, like metformin some scientists have already studied its role in this aspect.

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