European Review for Medical and Pharmacological Sciences 2021; 25: 4757-4761

Potential mechanisms of metformin-induced memory impairment

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Abstract. – Metformin is the most commonly prescribed drug for the treatment of type 2 diabetes mellitus. In addition to its ability to lower glucose levels, it has recently been reported to be potentially useful for the treatment of other conditions because of its anticancer activity, cardiovascular protective effect, neuroprotective effect, and efficacy in the treatment of polycystic ovary syndrome. However, long-term use of metformin may lead to side-effects such as memory impairment. Here, we critically review the effect of metformin on memory impairment and the potential molecular mechanisms of memory dysfunction to provide a reference for researchers and a better understanding of the side-effects of metformin.

Key Words:
Metformin, Memory impairment, Antitumor activity, Protein kinases.

Introduction

The biguanide metformin is the most commonly used oral hypoglycemic drug. It functions mainly by improving the sensitivity of insulin receptors to insulin, resulting in enhanced glucose uptake, and decreased hepatic glycogen synthesis[1,2]. Recent studies[3,4] have shown that metformin can cross the blood-brain barrier to improve energy metabolism and protect neurons from inflammation. Magnetic resonance imaging has shown that neuroinflammation and brain metabolic stress can lead to cognitive dysfunction[5,6]. Thus, it is hypothesized that metformin treatment will improve cognitive impairment.

Metformin has been shown to improve phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling to induce translocation of glucose transporter type 4 (GLUT-4) to the cell surface and facilitate glucose influx[7,8]. Several lines of evidence have revealed that metformin can improve memory impairment under some disease conditions. For instance, it has been reported to improve memory impairment caused by Alzheimer's disease (AD), Parkinson's disease (PD), diabetes, and chemo brain[9-12]. AD, PD, diabetes, and some chemotherapeutic agents such as doxorubicin (DOX) have been shown to reduce AKT activity, which is important for GLUT-4 trafficking[8]. Thus, it has been previously indicated that metformin administration could activate AMPK and thereby, increase AKT activation, leading to elevated GLUT4 trafficking to the cell surface, and a reduction in the hyperglycemic effect. By contrast, another study[13] showed that memory function impairment caused by DOX was not improved by metformin, which itself caused cognitive impairment.

Therefore, in this review, the mechanism of metformin-induced cognitive impairment will be discussed. While some studies have shown that metformin has beneficial effects on cognitive dysfunction, others indicated that metformin failed to rescue memory dysfunction. Furthermore, metformin has also been reported to alter protein expression or activities and mitochondrial function, which may contribute to memory impairment and decrease synaptic plasticity; these studies are the focus of this review (Figure 1).

Metformin and Behavioral Assessment

Behavioral evaluation is a psychological technique used to observe, describe, and explain the behavior of humans and animals. This approach is employed to determine and quantify and different factors, such as emotions and individual variables, that influence behavioral changes. Most of the tasks used in behavioral tests evaluate long-term or short-term memory function, with each task focusing on a certain pathway in the brain. For

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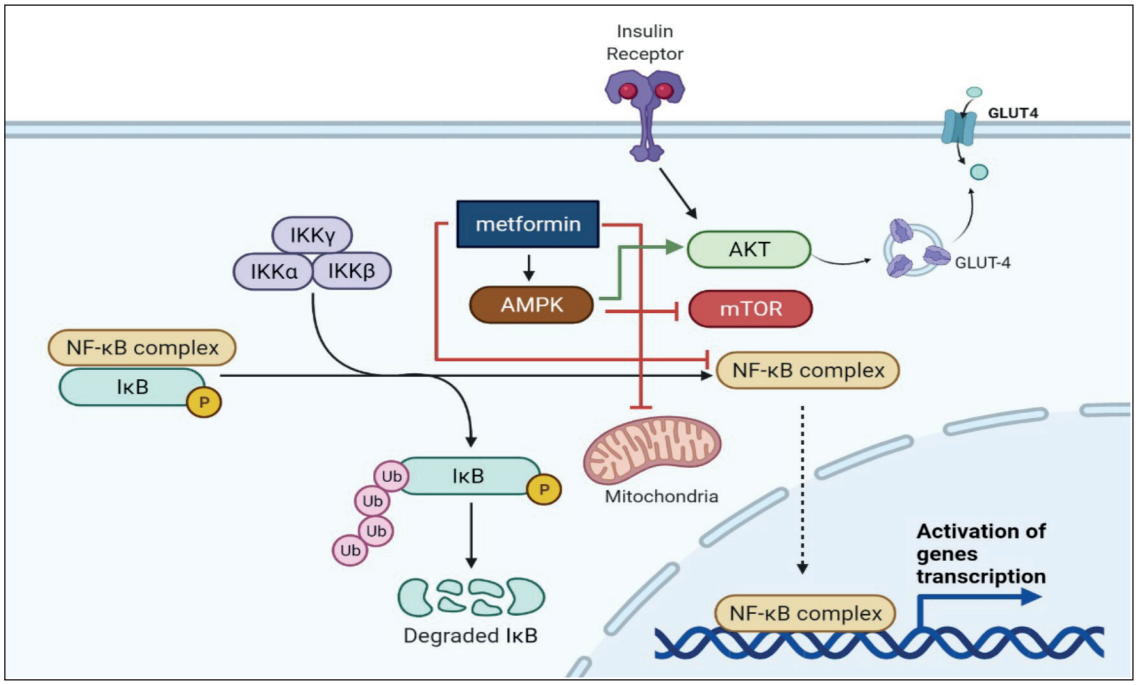

Figure 1. Mechanisms of metformin-induced memory dysfunction.

instance, the Y-maze and novel object recognition (NOR) tests are used to evaluate spatial memory function. These two tests involve hippocampus-dependent tasks, in which information passes through the hippocampus during memory formation. The Y-maze test is dependent on the dorsal hippocampus, whereas the NOR test depends on the ventral part of the hippocampus. Therefore, these tests are suitable for the investigation of potential mechanisms of memory impairment.

Metformin can improve memory impairment in AD, PD, diabetes mellitus, and chemotherapy-induced memory impairment[9-12]. However, chronic administration of metformin itself can result in memory impairment[13]. Here, we review the negative effect of metformin on memory function.

Metformin and Mitochondrial Dysfunction

Mitochondria are organelles found in most eukaryotic cells and play an important role in energy production, calcium regulation, cell metabolism, and synaptic transmission[14]. The energy produced by mitochondria is stored in the form of the small molecule adenosine triphosphate (ATP)[15]. Mitochondrial dysfunction is a known cause of cognitive impairment[16]. Long-term use of metformin can induce mitochondrial dysfunction through the inhibition of mitochondrial oxygen consumption by suppressing complex I activity[17], which could thus result in memory impairment. By contrast, metformin is reported to rescue mitochondrial dysfunction caused by diabetes and heart failure[18]. Based on these results, it is appeared that metformin has beneficial effect in mitochondrial function in case of some disease states that effect on the mitochondrial function; however, it causes mitochondrial dysfunction by its treatment for a long time.

Metformin and Protein Kinases

The Mammalian Target of Rapamycin (mTOR)

The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that is involved in many physiological processes, including cell proliferation[19]. The mTOR protein kinase exists in two different complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), each of which activates a different downstream signaling process. The mTOR complexes regulate numerous processes required for cell growth and metabolism, and function as signaling nodes that integrate cellular nutrient and stress status signals and induce appropriate cellular responses. mTORC1 activation is associated with spatial learning and fear conditioning, as well as long-

term potentiation, depression, and synaptic plasticity[20]. AMPK activation phosphorylates TSC2 and enhances TSC1/2 activity, thereby inhibiting mTORC1[21]. Metformin enhances AMPK activity, leading to mTOR inhibition and ultimately contributing to memory impairment[22]. In addition, mTOR regulates glutamate receptor subunit-1 (GluR1) expression, which is necessary for triggering memory formation[23]. Therefore, metformin could indirectly contribute to memory impairment through inhibition of the mTOR protein kinase.

Nuclear Factor Kappa B (NF-κB)

Nuclear factor kappa B (NF-κB) is a ubiquitously expressed transcription factor that has been identified in several regions of the brain including the hippocampus, cortex, and amygdala, where it is found inside the nucleus and is transcriptionally active[24]. NF-κB is activated by various stimuli, including cytokines, such as tumor necrosis factor alpha (TNF-α), growth factors, and bacteria or viruses, through the expression of stress response genes in many cells[25], as well as glutamate, amyloid beta peptide, oxidative stress, and membrane depolarization[26,27]. It is also involved in the degradation of IκB, thus permitting nuclear translocation of NF-κB for transcription of target genes. The role of NF-κB in the central nervous system is not fully understood; however, it is well established that NF-κB plays an important role in regulating synaptic plasticity and memory formation[29,30]. In addition, NF-κB controls spatial memory formation and synaptic plasticity by regulating the expression of protein kinase A (PKA) and the cAMP response element-binding protein (CREB) pathway, which ultimately enhances synaptogenesis[30,31]. NF-κB also plays an important role in regulating long-term potentiation (LTP) and long-term depression (LTD). NF-κB increases during the induction of LTP, which is impaired by the inhibition of NF-κB[31]. LTD is not induced when NF-κB is inhibited, indicating the importance of NF-κB in regulating synaptic plasticity and memory formation[31,32]. Ultimately, the ability of metformin treatment to inhibit NF-κB activity indicates its potential role in the mechanism of metformin-induced memory impairment[33,34].

Metformin and Thyroid Function

The thyroid hormones thyroxine (T4) and triiodothyronine (T3) are known to play vital roles in several biological functions, such as growth, development, and energy metabolism[35]. Thyroid hormones act on almost every cell in the body[36], and abnormal levels are associated with diseases including hyperthyroidism, hypothyroidism, and cretinism.

Thyroid hormones are synthesized in the thyroid gland under the control of the hypothalamic-pituitary-thyroid axis (Figure 2). This axis comprises the hypothalamus, which releases thyrotropin-releasing hormone (TRH). TRH then stimulates the anterior pituitary gland to release thyroid-stimulating hormone (TSH), which acts on thyrotropin receptors in the thyroid gland and regulates all the steps involved in thyroxine (T4) and triiodothyronine (T3) production. T3 and T4 inhibit their own production by feedback inhibition of both TRH and TSH production[38,39].

Once thyroid hormones are released into the bloodstream, they act through the thyroid hormone receptor (TR), which is a member of the nuclear receptor superfamily[40]. TR occurs in two isoforms, α and β, which are differentially expressed in different tissues. The α1 receptor is expressed mainly in the heart and skeletal muscles, whereas the β1 form is expressed mainly in the liver, kidney and brain[42]. Thyroid hormones regulate brain development, neurogenesis, synaptogenesis, and myelination[43,44]. Moreover, TRs are expressed at high levels in the hippocampus, the part of the brain responsible for memory formation[44]. Therefore, changes in thyroid hormone levels may be responsible for the alteration of hippocampal functions leading to the disruption of learning and memory processes and cognitive impairment[45].

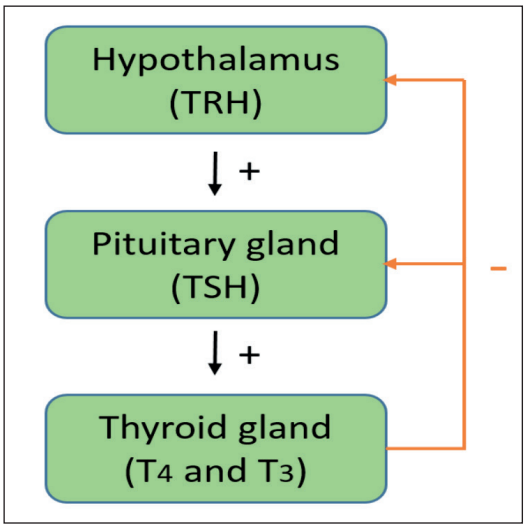

Figure 2. Representation of the hypothalamic-pituitary-thyroid axis with feedforward and feedback control loops.

Hence, neuroimaging studies[46,47] show that the structure and function of the hippocampus are altered in hypothyroidism. Interestingly, metformin results in alteration of thyroid functions through the reduction in the levels of TSH[48,49], which could ultimately affect the T3 and T4 levels. Therefore, alteration of thyroid hormone levels may be a potential mechanism of memory impairment caused by metformin treatment.

Conclusions

The studies considered in this review indicate that metformin treatment has certain beneficial effects, such as enhancement of memory function in several disease conditions. However, it is also reported that memory is impaired by long-term metformin treatment. It can be hypothesized that memory impairment occurs through deregulation of mTOR, NF-κB, or thyroid hormones.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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