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MINI-REVIEW ARTICLE

Metformin: A Growing Journey from Glycemic Control to the Treatment of Alzheimer's Disease and Depression

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Abstract: Metabolic stress, transduced as an altered cellular redox and energy status, presents as the main culprit in many diseases, including diabetes. However, its role in the pathology of neurological disorders is still not fully elucidated. Metformin, a biguanide compound, is an FDA approved antidiabetic drug generally used for the treatment of type 2 diabetes. The recently described wide spectrum of action executed by this drug suggests a potential therapeutic benefit in a panoply of disorders. Current studies imply that metformin could play a neuroprotective role by reversing hallmarks of brain injury (metabolic dysfunction, neuronal dystrophy and cellular loss), in addition to cognitive and behavioral alterations that accompany the onset of certain brain diseases such as Alzheimer's disease (AD) and depression. However, the mechanisms by which metformin exerts its protective effect in neurodegenerative disorders are not yet fully elucidated. The aim of this review is to reexamine the mechanisms through which metformin performs its function while concentrating on its effect on reestablishing homeostasis in a metabolically disturbed milieu. We will also highlight the importance of metabolic stress, not only as a component of many neurological disorders, but also as a primary driving force for neural insult. Of interest, we will explore the involvement of metabolic stress in the pathobiology of AD and depression. The derangement in major metabolic pathways, including AMPK, insulin and glucose transporters, will be explored and the potential therapeutic effects of metformin administration on the reversal of brain injury in such metabolism dependent diseases will be exposed.

Keywords. Metabolic Stress, Metformin, Alzheimer's Disease, Depression, AMPK Pathway, Insulin, Glucose Transporters.

1. INTRODUCTION

Metabolic stress is considered at the heart of numerous prevalent disorders, including type 2 diabetes (T2D) [1, 2]. Such type of stress stems from the imbalance between nutrient availability and energy expenditure, eventually culminating in an altered energy status within the cell [3]. In T2D, the abundance of glucose and lipids results in an overwhelmed cellular machinery, which ultimately leads to an aberrant cell function [4]. Metformin, used as a first-line oral antidiabetic drug, has shown great efficacy and safety profiles in the treatment of diabetic patients. This compound was proven to reduce the levels of circulating glucose and lipids and correct, to a significant extent, the metabolic disturbance in diabetes [5]. However, the effect of metabolic stress is not only limited to the peripheral organs such as the liver, skeletal muscles and adipose tissues, but it also extends to other organ systems, including the nervous system and the brain in particular [6].

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There is a growing body of evidence suggesting that metabolic stress solely, or in combination with genetic and environmental factors, among others, could provide the driving force for the development of brain disorders comprising Alzheimer's disease (AD) and depression [7, 8]. These data suggest a common mechanism between T2D, AD and depression. In that context, several studies describe diabetes as a prominent risk factor for the development of both AD and depression [9, 10]. Therefore, new lines of research focus on untangling the shared signaling mechanisms correlating T2D to AD and depression. Among these pathways, the AMPK signaling, which is thought to be the main intracellular fuel gauge in mammals [11], is being investigated. This pathway has been recognized as a direct target for metformin action, through its interaction with a wide array of upstream and downstream effectors such as insulin and glucose transporters (GLUT) in order to establish homeostasis within the cell [12-14]. However, the effect of AMPK activation is still poorly understood in the context of brain pathology, where metabolic stress constitutes a major compartment of the injury.

This review highlights the mechanism by which metformin improves metabolic disturbance, emphasizes the importance of metabolic stress in the development of AD and depression and more importantly, discusses the mechanisms by which metformin treatment relieves the cognitive and behavioral dysfunctions associated with the onset of these later neurological disorders.

2. METFORMIN: THE MECHANISMS OF ACTION

Several studies identify that activating the AMP-dependent protein kinase (AMPK) is the key target of metformin [13-17]. AMPK is a heterotrimeric serine/threonine kinase complex [18]. It consists of a catalytic α-subunit and regulatory β- and γ-subunits. AMPK is described as the main energy sensor and the master switch for the regulation of glucose and lipid metabolism, and it is expressed in a tissue-specific manner [13, 19, 20]. The AMPK pathway is of utmost importance for the metabolically active cells, such as the neurons, where high energy levels are constantly required for proper functioning [21]. Activation of AMPK occurs through a variety of signals including the AMP/ATP ratio, cellular stressors, hormones and exogenously through pharmacological intervention [22]. Metformin, the biguanide compound, is best known for its usage as the first line of intervention to enhance insulin sensitivity in metabolic disorders such as type 2 diabetes [23]. Upon its intracellular transport through the plasma membrane, metformin selectively inhibits the complex I of the mitochondrial respiratory chain in a weak and reversible manner, resulting in an increase in AMP/ATP ratio [24]. This in turn increases the phosphorylation of AMPK on its activation loop threonine 172, allowing it to exert its effect largely at three different levels: 1) reducing hepatic glucose production by decreasing gluconeogenesis and glycogenolysis, while augmenting glucose uptake via GLUT-1 translocation to the hepatocytes in an insulin receptor substrate-2 (IRS-2) mediated mechanism [25, 26]; 2) upregulating glucose utilization by peripheral organs such as the skeletal muscles. This process was suggested to comprise an enhancement in the tyrosine kinase activity of the insulin receptor, in glycogenesis and in GLUT-4 transporter number and activity [27-30]; 3) regulating lipid metabolism by reducing fatty acids oxidation while promoting their re-esterification, which is thought to improve both insulin secretion and sensitivity by minimizing the level of circulating free fatty acids. Metformin was also reported to decrease hepatic lipogenesis in an AMPK dependent mechanism [31-33]. Furthermore, the activation of AMPK by metformin leads to the inhibition of anabolic processes involving the mammalian target of rapamycin complex 1 (mTORC1) pathway, thus decreasing protein and lipid synthesis and dampening cellular growth, proliferation and survival [16, 34, 35].

Currently, there is an increasing body of evidence showing that metformin also acts through other pathways independent of AMPK, such as the alleviation of mitochondrial ROS production and decreasing inflammation through the specific inhibition of reverse electron transport RET- linked ROS production [11, 36]. These various functions performed by metformin advertise it as a potential therapeutic target for a panoply of diseases, presently AD and depression, where metabolic stress, in particular, is thought to play an important role in the pathology of these neurological disorders. Nevertheless, the divergence in the mechanisms of action of such compounds necessitates a careful and deep examination of the alterations in brain function brought about by the chronic exposure to such therapies.

3. METABOLIC STRESS IN AD AND DEPRESSION: A FEEDFORWARD MECHANISM OF BRAIN INJURY

Neurological disorders comprise a broad spectrum of highly debilitating pathological conditions that target the central nervous system (CNS) and affect millions of people worldwide. Among the most prevalent and devastating neurological disorders are AD and depression [37, 38]. Prominent features underlying the outcomes of such disorders include neuronal dystrophies, loss of function and cell death. These features share several mechanistic similarities at the subcellular levels, including abnormal protein aggregation, impaired axonal transport, programmed cell death and, more importantly, metabolic dysfunction [39, 40]. Till now, there is no cure to such disorders due to the limited understanding of the underlying pathogeneses [41]. However, previous findings from clinical and experimental work show that altered brain metabolism, probably through an AMPK dependent mechanism, is the core of these neurodegenerative disorders and others such as Parkinson's and Huntington's diseases [42-45]. Therefore, targeting the AMPK signaling pathway and its upstream or downstream effectors may hold promising and unrivaled therapeutic benefits for these brain defects.

3.1 Alzheimer's Disease

AD is the most prevalent form of neurodegenerative diseases and affects memory, cognition, and behavior. In the United States, AD is the sixth leading cause of death and accounts for around 60-80% of dementia cases and cognitive impairments [46]. Patients are diagnosed with AD by the visualization of two primary brain lesions encompassing the formation of extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) [47]. It is widely accepted that the etiology of AD is multifactorial and involves complex biological mechanisms. Of interest, metabolic disturbances and mitochondrial dysfunction are shown to be key players in the pathogenesis of this disease.

3.1.1. AD and Metabolic Disturbances

Recent data from clinical and experimental work suggest the presence of a link between AD and brain metabolic dysfunction. In fact, AD is now being referred to as type 3 diabetes due to the inability of the brain to efficiently utilize glucose for energy production and respond to critical trophic factors such as insulin [48]. In fact, recent epidemiological studies underline that metabolic syndromes, such as obesity and diabetes, can be regarded as dominant risk factors for learning deficits and cognitive impairments, similar to what is observed in the AD patients [49]. Furthermore, the intra-cerebroventricular (ICV) injection of Streptozotocin (STZ) drug in rodents induced neurodegenerative features accompanied by cognitive and memory impairments resembling those of AD [50-53]. In line with that, Frolich and co-workers found a reduction in the number of insulin receptors and in tyrosine kinase activity in the postmortem brains of AD patients [40, 54, 55].

With these caveats in mind, special attention is warranted to outline the role of insulin in the neuropathogenesis of AD. Previously, the brain was thought to be an insulin-insensitive organ. However, it is now well recognized that insulin is readily transported across the blood brain barrier (BBB). Also, insulin receptors are widely distributed on the neuronal synapses and astrocytes in specific brain regions such as the prefrontal cortex (PFC), amygdala and the hippocampus implicating a role of insulin in learning, memory and cognitive processes [56]. Moreover, positron emission tomography (PET) studies confirmed that insulin selectively influences regional glucose metabolism in neurons and astrocytes in rodent and animal studies [57]. Therefore, it is important to highlight the link between brain insulin impairments and neurodegeneration in AD. Indeed, insulin promotes the secretion of amyloid Aβ precursor protein (APP) and its trafficking to the plasma membrane, while decreasing its clearance [58]. In this context, hyperinsulinemia, which characterizes the first stages of insulin resistance, has been shown to mediate amyloidosis in the early stages of AD. On the other hand, reduced downstream activation of GSK-3β (Glycogen synthase kinase 3 beta), which is known to be regulated by insulin, mediated tau hyperphosphorylation, another major hallmark of brain injury in AD [59]. Moreover, Schubert M and co-workers showed that IRS knockdown resulted in tau hyperphosphorylation [60]. Furthermore, data from the human brains of AD patients and intracerebral STZ injected animal model indicate a disrupted gene expression of inflammatory and apoptotic markers suggesting that insulin impairments mediate neuronal loss and brain atrophy in AD [61]. Animal models of intracerebral STZ induced AD have also shown reduced levels of Acetylcholine (Ach) and increased expression of Acetylcholine esterase enzyme (AchE), thus a disrupted cholinergic system which mediates cognitive impairments in AD [62].

Special attention has also been granted to glucose uptake and its utilization in brain metabolism. Glucose in the brain is transported intracellularly through insulin insensitive glucose transporters (GLUT) and sodium glucose cotransporters (SGLT), that are widely distributed in specific brain regions implicated in cognitive processes, and it is metabolized through oxidative phosphorylation. The major glucose transporter found in neurons is GLUT-3 [63]. However, neurons also express GLUT4, which is insulin sensitive, in brain regions related to cognitive function such as the hippocampus [64]. Through insulin-phosphoinositide 3 kinase (PI3K)-Akt signaling, GLUT-4 is translocated to the plasma membrane of neurons, especially during periods of high energy demands [65]. GLUT-1, on the other hand, is mainly found in glial cells and endothelial cells of the blood brain barrier [66]. In the brain of AD patients, reduced expression of major GLUTs has been observed [57, 67, 68].

3.1.2. AD and Mitochondrial Dysfunction

From a different standpoint, the disruption of energy processing strongly implies the involvement of mitochondrial dysfunction at the core of AD pathogenesis. Altered mitochondrial infrastructure was reported in AD brains more than 40 years ago, then confirmed and further elaborated on in later studies [69-72] For instance, AD brains exhibited a reduced number and an altered function of mitochondria caused by a disruption in electron transport chain (ETC) enzymes such as pyruvate dehydrogenase complex and cytochrome c [73, 74]. The importance of mitochondria in AD led to the suggestion that mitochondrial dysfunction lies upstream of Aβ accumulation and might be the instigator of the injury cascade in this disorder. That was supported by extensive *in vitro* and *in vivo* studies showing that disrupted mitochondrial bioenergetics shifts amyloid-β protein precursor (AβPP) towards amyloidogenic pathways [75-77]. However, this theory was challenged, and mitochondrial malfunction was considered to occur secondary to amyloid aggregation, with mitochondrial respiratory chain suggested to specifically mediate Aβ toxicity [78-80]. Interestingly, enhanced interaction between AD-associated protein aggregates and the mitochondria has also been described. For example, APP and Aβ fragments were shown to be trapped on the outer mitochondrial membrane, blocking its permeability transition pore (mPTP) and leading to cognitive deficits through the accumulation of toxic oxidative species and cell apoptosis [79, 80]. Tau protein is also described to block mitochondrial dynamics through the interruption of the microtubule, tracks responsible for mitochondrial intracellular mobility [81]. The significance of mitochondrial changes in AD is continually growing and targeted therapies against such organelles have been postulated by many as a valid therapeutic approach for the improvement of cognitive, behavioral and molecular changes associated with the onset of the disease.

Taking these observations together, and from a mechanistic perspective, the physio-pathological alterations observed in AD could be potentially overcome by the use of metformin.

3.1.3. The Neuroprotective Role of Metformin in Alzheimer's Disease

Despite years of experimental research and clinical trials in AD, only few drugs have attained FDA approval; however, they only provide temporary relief and have serious side effects [82]. This has led researchers to look into other alternatives in order to find more effective therapies for AD. With the discovery of potential links between AD and metabolic disturbances within the brain [83, 84], investigators considered the use of antidiabetic drugs such as metformin for the treatment of brain insulin resistance in AD [85]. In a large case-control study, Imfeld *et al.* showed that long-term users of metformin had a slightly higher risk of developing AD as compared to non-users, with no consistent trend with regards to metformin dosage [86]. Contradicting results have been revealed from another study, where in a sample of diabetic participants (n=126), patients who were treated with metformin showed worse cognitive performance than those not taking metformin; however, this was a small-scale study that did not take into account the dose and duration of metformin use [87]. In another pooled analysis of 3,590 participants with diabetes, metformin use in diabetic patients showed no significant association with the risk of dementia or other measures of cognitive performance [88].

Despite these confounding findings, metformin was found to reduce the risk of dementia in other studies. In a representative cohort study, participants with T2D were shown to have an increased risk of developing dementia when compared to controls; however, diabetic participants who were treated with metformin showed a reduced risk of dementia [89]. In accordance with the previous study, in a more recent cohort study based in Taiwan, the hazard ratios suggested a lower risk of developing dementia in T2D patients who were treated with metformin, specifically when treated for longer than two years [90]. Following non-diabetic participants aged 65 years and over to study the onset of T2D and the development of dementia, Cheng *et al.* found that T2D patients who had been treated with metformin or sulfonylureas for a long period had a significantly lower risk of developing dementia [91]. In a later cohort study on US veterans with T2D, new users of metformin or sulfonylurea were followed over a period of 5 years to assess the onset of dementia, and metformin use was associated with a reduced risk of subsequent development of dementia as compared to sulfonylurea usage [92]. In fact, a pilot study on AD prevention was conducted where patients with amnestic mild cognitive impairment (aMCI), which usually progresses to dementia, were treated with metformin. Preliminary evidence suggested improvements in the total recall of the Bushcke Selective Reminding Test (SRT) in the metformin-treated participants compared to the placebo group. However, plasma Aß levels and glucose uptake levels by the brain did not show significant changes [93]. In another placebo-controlled study on non-diabetic subjects with mild cognitive impairment, metformin treatment was associated with improvements in executive functioning, learning, memory and attention [94].

Interestingly, studies have shown that metformin can cross the blood-brain barrier and thus act centrally to exert its neuroprotective function; however, its mechanism of action within the CNS is still not completely understood [95, 96]. Despite all of these findings, further clinical trials are warranted to address the role and effect of metformin on AD patients, independent of T2D. A closer look should be designated to the potential effect of metformin on cerebral blood blow (CBF), which forms the main component of brain injury in AD. So far, these studies are lacking, and the available data are inconclusive [94]. Thus, investigating the interrelationship between AD and metformin administration on CBF would help in untangling the mechanism of action of such compounds under neuropathological conditions.

In accordance with the clinical findings, several *in vitro* studies have been conducted to show the potential benefits of metformin on models of AD. In an experimental model of type 3 diabetes on cultured neurons, metformin decreased the levels of phosphorylated tau (pTau), Aß and Acetylcholine esterase enzyme (AchE), which are major features of AD [97]. In addition to that, metformin was found to inhibit apoptotic pathways induced by Aß toxicity in cultured hippocampal neurons [98]. However, in neuroblastoma cells, metformin was shown to increase APP expression, oxidative stress and mitochondrial dysfunction, all of which are the main pathological features of AD. These effects were ameliorated by the addition of insulin along with metformin [99] suggesting that metformin action is dependent on the availability and levels of insulin.

In a mouse model of T2D, metformin attenuated AD-like pathologies in the brain, such as the increase in pTau levels and the decrease in synaptic protein levels [100]. In addition to that, metformin was shown to interfere with the assembly of the Midline 1-Protein phosphatase 2A (MID1-PP2A) complex, decreasing the levels of the amyloidogenic enzyme beta-secretase 1 (BACE1), and thus the synthesis of Aß proteins [101]. It was also shown to decrease the phosphorylation of tau protein at AD-specific phosphorylation sites in a similar manner [102]. In an STZ induced mouse model of sporadic AD, treatment with metformin protected spatial learning and memory in a dose-dependent manner [103]. In a different mouse model of sporadic AD, metformin improved learning and memory in a variety of behavioral tests through a decrease in Aß and pTau [104]. On the other hand, metformin treatment was shown to have a puzzling effect on tauopathies. In a mouse model of tauopathy, treatment with metformin was able to promote Tau aggregation, which has a negative impact on neurons, while simultaneously decreasing Tau phosphorylation [105]. In a scopolamine-induced AD model of male rats, treatment with metformin ameliorated cognitive deficits through blocking inflammatory processes and oxidative stress. Moreover, it decreased the total level of Akt but increased its phosphorylated form which results in lower levels of phosphorylated tau [106]. In a recent study on transgenic *Caenorhabditis elegans* expressing human Aß, treatment with metformin was able to block metabolic defects associated with Aß toxicity prolonging the lifespan of the *C. elegans* [107].

3.1.4. AMPK, Insulin and Glucose Transporters as Mediators of Metformin Effect in AD

AMPK signaling was suggested to contribute to AD pathology due to its regulatory roles on Tau and Aß proteins [108]. In human neuronal stem cells, metformin activation of AMPK resulted in protection against Aß-induced mitochondrial dysfunction [109]. Conversely, in neuronal cell cultures expressing the human APP gene, treatment with metformin was shown to increase levels of Aß and beta-secretase 1 through activation of the AMPK pathway; however, the addition of exogenous insulin following treatment with metformin reversed these results [95]. In another study on a neuronal model of insulin resistance, metformin was shown to enhance AMPK phosphorylation while exhibiting beneficial effects on AD-like pathologies [97]. This indicates that the neuroprotective effects of metformin in the potential treatment of AD are AMPK dependent, and the effects of stimulating this signaling pathway can vary depending on the manner of its activation; these contradicting results may be due to variations in cell types and culture conditions [110]. In

2012, Wang and colleagues showed that metformin administration enhances neurogenesis and spatial learning through an atypical protein kinase C-CREB binding protein (aPKC-CBP) signaling downstream of AMPK [111]. In a study on female AD mice, metformin decreased Aß accumulation, neuroinflammation, spatial memory deficits and neuronal loss in the hippocampus through enhancing hippocampal AMPK signaling on mTOR and nuclear factor kappa B (NF-kappaB) [112]. However, another study revealed that the beneficial effect of metformin is sex-specific, occurring only in female but not in male AD mice [113]. These results disagree with previously mentioned studies that showed positive effects of metformin on cognition in male murine models. In order to better understand these results, further testing should be conducted on males and females separately in preclinical and clinical settings.

Metformin may also be acting on the insulin signaling pathway independently of AMPK signaling [108]. Peripherally, metformin treatment has been shown to reduce levels of insulin [114] and inflammatory cytokines [115]. Thus, it is suggested to have a beneficial role among people at risk of developing AD, such as T2D patients, due to its ability to reverse hyperinsulimia, a major feature of insulin resistance [89, 90]. More importantly, and since metformin can cross the blood-brain barrier, it may also be working directly on insulin signaling within the brain, which makes metformin treatment of greater importance since it may ameliorate altered brain metabolism of glucose [116]. In an *in vitro* study on insulin-resistant neurons, impairments within the insulin signaling pathway, such as decreased IRS-1, protein kinase C and Akt phosphorylation, were ameliorated following treatment with metformin [97]. In the SAMP8 mouse model of AD, decreased levels of phosphorylated GSK-3β, which is indicative of impaired insulin signaling, were ameliorated by treatment with metformin [104]. Collectively, these results elucidate the actions of metformin on insulin signaling and its downstream effectors in the central nervous system.

Impairments in glucose uptake and utilization by the brain are principal features of AD that are detected at early stages of degeneration [83], and are accompanied by a decrease in glucose transporters [117]. Interestingly, metformin has been shown to increase the translocation of glucose transporters to the plasma membrane, and thus increase total glucose uptake [118, 119]. In a model of Aß toxicity in *Drosophila melanogaster*, the induced overexpression of GLUT1 led to an increased glucose uptake, which ultimately alleviated Aß toxicity. These results were paralleled when the flies were treated with metformin [120] which could be an indication of its activity on glucose transporters and glucose uptake in neurons. However, further studies are warranted to elucidate the possible targeted action of metformin on glucose transporters, specifically within the CNS. These studies should take into account all the major glucose transporters within the brain while utilizing higher animal models.

Although these studies have presented diversified results, yet they favor the positive outcomes of targeting altered brain metabolism by metformin to alleviate AD pathology. There is an increasing body of evidence suggesting that metformin can sensitize neuronal insulin resistance, which is a major contributing factor of AD. However, in light of the conflicting evidence for the effects of metformin on AD, long-term, large-scale clinical trials should be conducted to assess its effectiveness as an early intervention strategy for AD. More importantly, these studies should encompass the use of varying doses of this compound in order to be able to determine the biosafety and ensure efficient delivery to the injured brain of AD patients.

3.2. Depressive Disorders: The Role of Metabolic Stress

Psychiatric disorders, particularly depressive disorders, are common mental illnesses that share clinical manifestations similar to neurodegenerative diseases such as declines in hippocampal volume and neurogenesis, disrupted neuronal circuitry, retracted dendritic processes and neuronal loss [121-123]. According to the American Psychiatric Association, major depressive disorder (MDD) is marked by either an irritable mood, decreased interest/pleasure or both [124]. Advances in research have promoted several theories on the possible mechanisms through which depression develops, such as changes in the neurotransmitter system, dysregulation of the immune and endocrine systems. However, these theories have been disregarded due to the fact that conventional antidepressant treatments used are effective in only 50% of patients [125, 126]. Therefore, it is currently well accepted that the pathogenesis of depression is multifaceted, and it is an interaction of genetic and environmental factors that contributes to the pathology of depressive disorders. Intriguingly, metabolic derangement appears to be one important instigator underlying depression [127].

Recent data have widened the field substantially to consider metabolic disruption as the chief mediator of depression [128]. The earliest evidence of metabolic stress in depression from clinical data showed a close association between emotions and metabolic disorders such as insulin resistance and led to the classification of depression as metabolic syndrome type II [129, 130]. This hypothesis has gained particular attention primarily after numerous findings highlighting the beneficial roles of insulin in emotions and affection through the regulation of the hypothalamic pituitary adrenal (HPA) axis, neurogenesis, synaptic plasticity and neurotrophic factors [131, 132]. Moreover, a reduction in insulin receptors and their activity has been well documented in depressed brain sections, marking another feature of brain insulin resistance in such diseases [133]. Other insights come from the fact that intracerebral injection of STZ in animals produced depressive-like symptoms, while insulin treatment reversed these symptoms, underlining the role of insulin in the development of depression. Imbalances in brain glucose metabolism have also been suggested to participate in the pathophysiology of depression, since the presence of depressive symptoms is associated with a reduction in GLUT transporters in the hippocampus, PFC and amygdala [134, 135]. Interestingly, other studies reported altered glucose metabolism in depressed rodents paralleled with increased glycolysis enzyme phosphofructokinase and reduction in Krebs cycle's enzyme pyruvate dehydrogenase [136].

Besides insulin resistance and altered glucose metabolism, major attention is given to the role of mitochondrial bioenergetics in the pathogenesis of depression. In fact, mitochondria play a key role in cellular functions which, when interrupted, lead to disturbed ATP production, calcium accumulation, ROS overproduction and dysregulated cell death [137-139]. Increasing evidence suggests a substantial link between mitochondrial perturbations and depression in clinical studies [140, 141]. In rodent studies, depressive-like symptoms were also associated with mitochondrial dysfunction represented by diminished stage 3 (ST3) oxygen consumption rate in the cortices, hippocampi and hypothalami of CMS exposed mice and altered mitochondrial membrane potential [142, 143].

Altogether, these studies suggest the importance of relieving metabolic disturbance as a potential therapeutic approach for neurological disorders, including depression. With this respect, the use of selective antidiabetic drugs could be beneficial due to their efficacy in reducing the alterations in the metabolic profile similar to that provoked by diabetes. In the following section, we will discuss the efficiency of metformin, commonly known as an insulin sensitizer, in reversing metabolic injury in depression.

3.2.1. Is Metformin, the New Generation Antidepressant?

Although major advances have been put forward in the field, no satisfactory treatments for depression are available till now [144, 145]. First-line agents used to treat depression include selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Other antidepressant classes are also found such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). However, these antidepressant drugs hold several limitations. For example, monoaminergic drugs may take several weeks or even months to elicit a therapeutic response. Preclinical and clinical findings demonstrate that glutamatergic agents produce a more rapid and long-lasting anti-depressant effect, but these drugs have limited efficacy and high resistance rates in around 20-30% of patients with depression [146]. On another level, long-term antidepressant treatment frequently leads to metabolic abnormalities such as body weight gain, hyperglycemia, elevated fasting glucose, hyperinsulinemia, insulin resistance, and dyslipidemia [147]. Thus, there is an urgent need to develop novel drugs or approaches for the treatment of depression [148]. This was when a new line of research was initiated to assess the effects of glucose-lowering drugs, traditionally used in the treatment of T2D, on mental health outcomes since brain-based disorders and diabetes mellitus share common molecular targets [149].

Accumulating evidence shows that metformin holds numerous health benefits in several neurological diseases [150]. However, its effect on the amelioration of depression is still debatable [151]. Several clinical and experimental studies demonstrate its antidepressant effects. For instance, a clinical cohort of 41,204 male veterans aged 74.6 years (SD=5.8years) with T2D exhibited a reduced risk of developing cognitive impairments and depression as well as several age-related morbidities (cancer, cardiovascular disease, frailty) upon treatment with metformin [152]. Consistently, Guo and colleagues showed that chronic treatment with metformin for 24 weeks improves cognitive performance and glucose metabolism, and decreases the severity of depressive symptoms in depressed patients with T2D [153]. In line with these findings, Chen *et al.* reported that overweight status and poor physical capabilities were risk factors for depression in elderly diabetic patients[154]. Interestingly, metformin was a protective factor against depression in these patients [154].

Furthermore, studies on experimental animals with depressive-like symptoms support the role of metformin as a mood-stabilizing agent. Indeed, the administration of metformin in rats for a period of 11 days significantly decreased depressive-like behaviors and increased the levels of neurotransmitters involved in depression, including norepinephrine and serotonin levels in the brain [155]. Likewise, metformin, used at increasing doses, decreased methamphetamine-induced (METH) behavioral disturbances in a dose-dependent manner [156]. Furthermore, this treatment counteracted the development of depressive-like behaviors in mice, exposed to social defeat stress when administered alone, or in combination with fluoxetine, a widely used antidepressant from the selective serotonin reuptake inhibitor (SSRI) family [148]. In that case, metformin exerted its anti-depressant effects on chronic restraint stress mice model in a dose and time-dependent manner [150], and this effect was a fast, and long-acting one (effect seen within hours and lasted for at least five days after a single injection) [150]. The beneficial effect of metformin shown in different animal models with depressive-like behavior was linked to an amelioration in inflammation, oxidative stress, synaptic plasticity, and neurogenesis [148, 157, 158]

At the molecular level, metformin triggers a chain reaction to initiate the anti-depressant effects. Under physiological conditions, stress exposure leads to the activation of the HPA axis and the elevation of glucocorticoids (GCs), which regulates the activity of the HPA axis through a negative-feedback mechanism involving the glucocorticoid receptor (GR) in the brain. However, stress causes impaired GR function, loss of negative feedback, and a sequential alteration in the HPA axis function. Moreover, hyperactivity of the HPA axis increases glucocorticoid release, which in turn reduces serotonin synthesis. A similar reduction in central serotonin availability can be mediated by diabetes-induced oxidative stress and inflammation in the brain [45, 158].

The intracellular energy metabolism involving the AMPK pathway may explain the depressive behaviors induced by chronic stress [148]. In the context of depression, decreased phosphorylation and the inactivation of AMPK are associated with depressive-like behaviors in rats and mice exposed to chronic stress. In the periphery, depending on the tissue, the regulatory function of GCs with respect to the AMPK pathway appears to be divergent. For instance, GCs decrease the activity of AMPK in the adipose tissue and heart, while it promotes AMPK activation in the liver and hypothalamus [45]. Besides, AMPK can regulate glucocorticoid receptor function through the p38 mitogen-activated protein kinase (MAPK) pathway. However, the relationship between GCs and AMPK in the CNS requires more studies [45]. Astrocytes are an essential source of ATP and neurotrophins, which maintain the normal function of neurons. Astrocytes play an important role in neuropsychiatric disorders, such as major depression and schizophrenia. Yuan *et al.* investigated the role of AMPK in GCs stress-induced down-regulation of GR in cultured rat prefrontal cortical astrocytes showing a link between the decrease in the expression of GR and AMPK inactivation [45]. Furthermore, the inactivation of AMPK was shown to occur in a glucocorticoid-inducible kinase1 (SGK1) dependent mechanism, which in turn promotes the activation of histone deacetylase 5 (HDAC5), resulting in decreased expression of GR after chronic exposure to GCs. More importantly, the activation of AMPK reverses GCs' stress-induced depressive behavior and GR down-regulation [45]. Moreover, the mechanism of metformin-induced effects was suggested to involve an upregulation in the expression of the brain-derived neurotrophic factor (BDNF) by increasing histone acetylation at the BDNF promoter level, which is attributed to the activation of AMPK and cAMP-response element-binding protein (CREB) in the hippocampus [148, 156]. The use of Compound C (AMPK inhibitor) to interfere with metformin treatment of primary cultured hippocampal neurons showed that metformin mainly mediates its beneficial effect in an AMPK- dependent mechanism. This work indicates that the metformin treatment significantly enhanced the number of dendritic branches in the primary hippocampal neurons, an effect entirely blocked by Compound C treatment [148]. Moreover, inhibition of AMPKα by compound C or knockdown of AMPKα in the hippocampus abolished the antidepressant-like effect of metformin, indicating that hippocampal AMPKα is necessary for the effect provided by metformin [150]. The neural circuitry responsible for depressive-like behavior involves several brain regions, including the medial PFC, hippocampus, and multiple components of the limbic system. Thus, it will be of interest to determine whether additional brain regions, besides the hippocampus, participate in the metformin-mediated effect. Interestingly, Soliman and colleagues demonstrated that the cerebral cortex of reserpine-treated (used to induce chronic depression in non-diabetic animals) rats comparably showed shrunken pyramidal cells surrounded by empty spaces. Dilated congested blood vessels were also observed in these brain regions [158].

In addition, the effect of metformin, especially in high doses, also extends to the cAMP-response element-binding protein (CREB), where Keshavarzi *et al.* have shown that this drug can inhibit METH-induced decrease in CREB protein expression and phosphorylation, thus promoting an increase in BDNF production in METH treated rats. Moreover, high doses of metformin (100 and 150mg/kg) can inhibit METH-induced increase in GSK3 and decrease in Akt protein expression and phosphorylation [156]. The effect of metformin on these pathways triggers the formation of a neuroprotective barrier to rescue cell survival under depressive conditions [156].

Furthermore, impaired insulin signaling is of interest since insulin resistance has been hypothesized to occur in the brains of major depressive disorder patients [149]. Clinically, a combination of fluoxetine and metformin was more effective than fluoxetine alone in ameliorating the depressive phenotype after one week of treatment. This combination was associated with an increase in IGF2 (Insulin-like growth factor 2) mRNA expression and enhanced long-term potentiation, specifically in the dorsal hippocampus, at the end of treatment [159]. The findings of Erensoy *et al.* also suggest that metformin enhances insulin sensitivity and improves mood both in adolescents and adult women with polycystic ovary syndrome, who are known to develop insulin resistance [160].

Metformin may also act by decreasing circulating branched-chain amino acids (BCAA) levels to favor tryptophan availability in the brain. These two molecules are thought to share the same transport protein through the blood brain barrier referred to as the large neutral amino acid transporter 1 (LAT1) [161]. Zemdegs and colleagues hypothesized that chronic exposure to a High fat diet (HFD) could raise plasma BCAA concentrations sufficiently to limit the uptake of tryptophan through LAT1 as a result of the competition between these amino acids and tryptophan, hence limiting serotonin synthesis throughout the brain [161]. Interestingly, metformin administration favored serotonergic neurotransmission in the hippocampus and promoted antidepressant-like effects in high fat diet-fed mice [161]. Since changes in plasma BCAAs are known to limit tryptophan availability in the brain, Zemdegs *et al.* also provided evidence that partial deficiency of BCAAs in the diet is sufficient to exert antidepressant-like activity [161].

Despite all of these findings, the mechanism of action of metformin in the context of depressive disorders is still not fully elucidated. Current studies also suggest an enhancement in neuroinflammatory and oxidative profile in animal models of depression upon treatment with metformin [155, 157, 158]. It was also recently reported that metformin can permeate the pituitary gland, frontal cortex, and hippocampus after chronic oral administration and exert anti-inflammatory and neuroprotective effects in the brain in a glucagon-like peptide 1 (GLP-1) dependent mechanism in a chronic unpredictable mild stress (CUMS) mouse model [162]. Furthermore, metformin was reported to peak 6 hours after oral administration in the brain of Wistar rats, with the brain to plasma ratio of 0.99, indicating a high BBB penetrance and an ability to efficiently reach the brain to perform its action [163]. Besides its effect on GLP1 activity enhancement, the role of metformin in the activation of antioxidant defense and the increased activity of antioxidant enzymes was also suggested. This type of activation could be involved in neuroprotection against some neurodegenerative situations [156].

Given the complexity of the disorder, the current data on the beneficial effect of metformin in depression (Fig. **1**) need further verification and more elaborate control of the experimental variables in order to be able to prove the efficacy of metformin in the treatment of such diseases. One important factor to be taken into consideration is the sex difference, knowing that the response to treatment in mental disorders is roughly gender-specific. It is also of utmost importance to lay more attention on the dose of metformin required to produce a beneficial effect clinically while ensuring the avoidance of any potential side effects.

CONCLUSION

The advancement in science driven by the abundance of research screening tools led to the characterization of alterations in diverse mechanistic pathways, which altogether culminate in cellular injury leading to various pathologies (Fig. **2**). This encouraged the repurposing of certain drugs for the treatment of atypical diseases thought to share common mechanisms of injury. With this respect, metformin is advocated as a potential treatment for some neurological disorders such as AD and depression. Till now, most of the reviewed studies support the use of such compounds for the alleviation of brain dysfunction and the behavioral alterations that accompany the neural injury. However, the use of metformin for the treatment of such pathologies still needs further investigation, especially in relation to the safety of such compounds and its delivery to the central nervous system, in addition to the appropri-

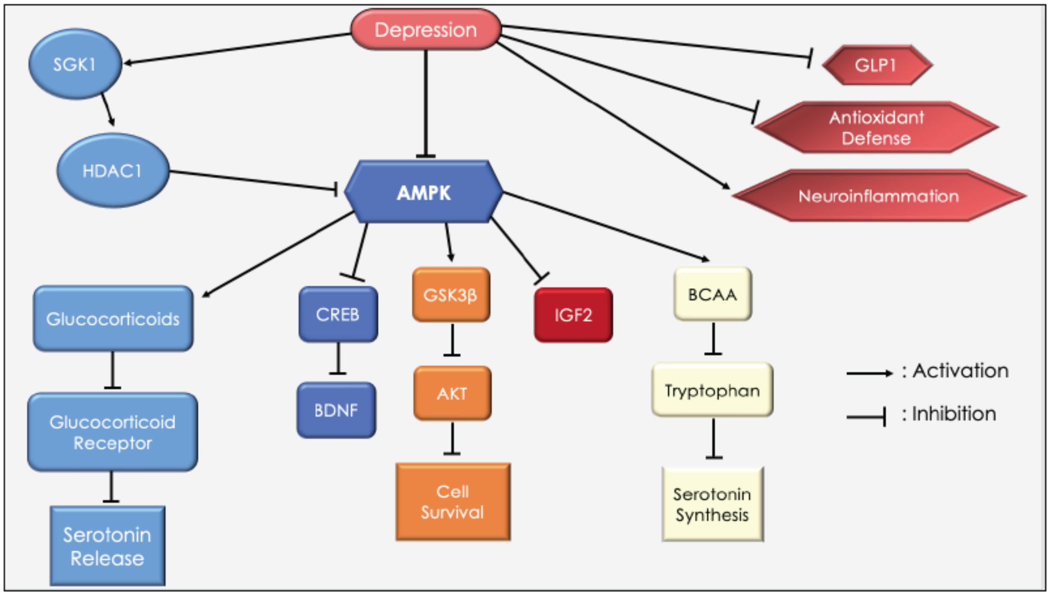

Fig. (1). Suggested molecular targets of metformin in depressive disorders. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

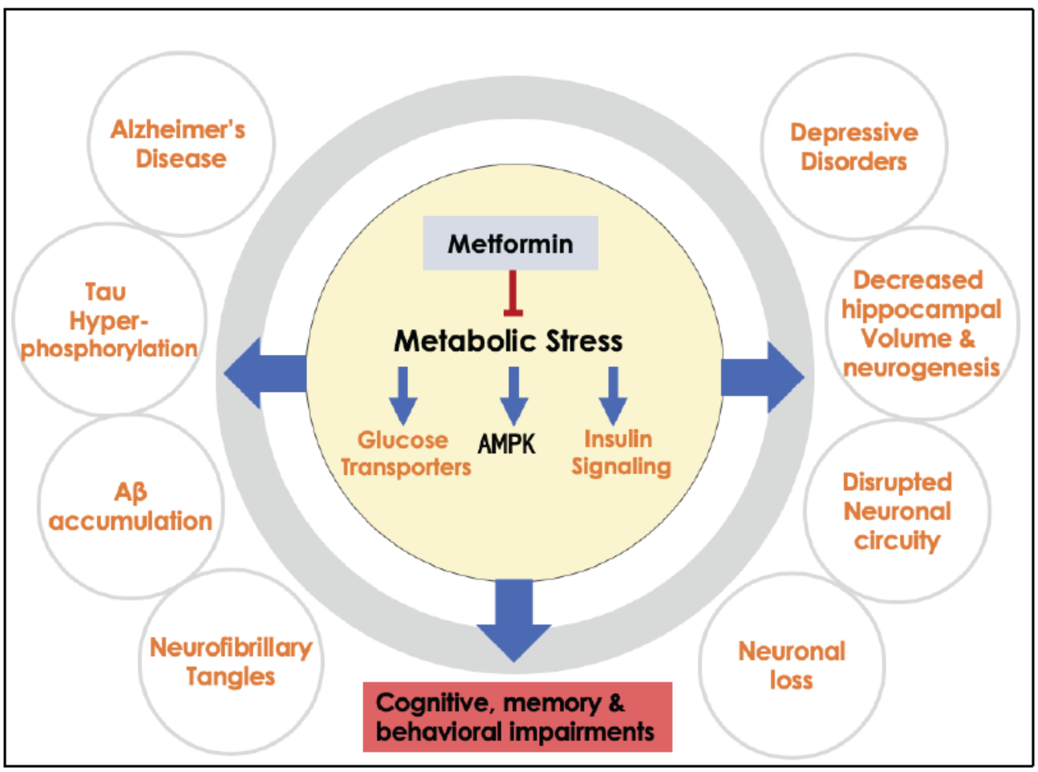

Fig. (2). The suggested role of metformin as a potential treatment for AD and depression. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

ate doses that are required to produce its beneficial effects, particularly in more advanced stages of the illness.

LIST OF ABBREVIATIONS

T2D	=	Type 2 diabetes
AD	=	Alzheimer's disease
ROS	=	Reactive oxygen species
AMPK	=	Adenosine monophosphate-activated protein kinase
GLUT	=	Glucose transporter

ATP = Adenosine triphosphate
IRS = Insulin receptor substrate
Aβ = Amyloid beta
STZ = Streptozotocin
APP = Amyloid precursor protein
GSK-3β = Glycogen synthase kinase 3 beta
BBB = Blood-brain barrier
CNS = Central nervous system
pTau = Phosphorylated tau
CREB = Cyclic AMP response-element binding protein
HPA = Hypothalamic pituitary adrenal axis
METH = Methamphetamine
GC = Glucocorticoid
GR = Glucocorticoid receptor
BDNF = Brain-derived neurotrophic factor
PFC = Prefrontal cortex
BCAA = Branched-chain amino acids

AUTHORS' CONTRIBUTIONS

AAE conceived and designed the review article and approved the final version to be submitted. MEM, LMA, LA and CS performed the literature review and wrote the manuscript.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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