IJMPR 2020, 4(4), 145-150

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

A REVIEW ON CNS ACTIVITY OF METFORMIN WITH SPECIAL REFERENCE TO ALZHEIMER'S DISEASE

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Received on: 13/07/2020
Revised on: 03/08/2020
Accepted on: 24/08/2020

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ABSTRACT

The treatment of neurodegenerative disorders are major concern in medical field. Nowadays symptomatic treatment are preferred. Metformin has long since been used to treat type 2 Diabetes Mellitus. In vitro and in vivo studies shows beneficial effect in treatment of neurodegenerative diseases such as Alzheimer's disease. This review discusses CNS Activities of Metformin in Alzheimer disease.

KEYWORDS: Alzheimer's disease, Metformin, CNS Activities of Metformin.

INTRODUCTION

Alzheimersdisease

Alzheimer's disease (AD) is the most common neurodegenerative disease, with 45 million people worldwide affected.AD is characterized by progressive memory loss and decline of cognitive function. It is a devastating neurodegenerative disorder, with aging, genetic ,and environmental factors contributing to its development and progression.[1]

Riskfactors

Age

The greatest known risk factor for Alzheimer's is increasing age .Most Individuals with the disease are 65 and older. One in nine people in this age group and nearly one-third of people age 85 and older have Alzheimer's.

Family history

Another risk factor is family history. Research has shown that those who have a parent, brother or sister with Alzheimer's are more likely to develop the disease than individuals who do not. The risk increases if more than one family member has the illness.

Familial Alzheimer's and genetics.

Two categories of genes influence whether a person develops a disease: risk genes and deterministic genes. Deterministic genes directly cause a disease, guaranteeing that anyone who inherits one willdevelopadisorder.Researchershavefoundseveralgen esthatincrease theriskofAlzheimer's. APOE-e4is thefirstriskgeneidentifiedandremains the one with strongest impact .Other common forms of the APOE gene are APOE-e2and APOE-e3.Everyone inherits a copy of some form of APOE from each parent.[2,3]

Symptoms that affect memory, awareness, language, judgment, andan individual's ability to plan, organize and carryout other thought processes.

Behavioural

A group of additional symptoms that occur—atleast to some degree—in many individuals with Alzheimer's. Individuals with the disease may develop wandering impulses at any stage.[2]

Stagesofdisease

Early-stage Alzheimer's

In the early stage of Alzheimer's a person may function independently. He or she may still drive, work and be part of social activities. Despite this, the person may feel as if he is having memory lapses ,such as forgetting familiar words or the location of everyday objects .Common difficulties includes;

- Trouble remembering names when introduced to new people. »Challenges performing tasks in social or work settings.
- Forgetting material that was just read.
- Losing or misplacing a valuable object.

Middle-stageAlzheimer's
Middle-stage Alzheimer's is typically the longest stage and can last for many years. As the disease progresses the person with Alzheimer's will require a greater level of care .You may notice the person with Alzheimer's confusing words

Symptoms
- Forgetfulness of events or about one's own personal history
- Confusion about where they are or what day it is.
- The need for help choosing proper clothing for the season or the occasion.
- Personality and behavioural change

Late-stageAlzheimer's
Experience changes in physical abilities ,including the ability to walk, sit and eventually swallow(2,3)

PATHOPHYSIOLOGY
Alzheimer'sdisease(AD)isadevastatingneurodegenerati vedisorder,with aging,genetic, and environmenta lfactorscontributingtoitsdevelopment andprogression. ADisnotonlycharacterizedbyp athologicaldeposition of Apeptidesand neurofibrilla rytanglesbutisal soassociatedwithmicroglia mediated inflammation and dysregulate lipid homeostasis and glucose metabolism Amyloid peptides are derived from sequential proteolytic cleavages of full-length amyloid precursor protein (APP)by-secretase (BACE1) and-secretase. Full-length APP can undergo alternative processing by-secretase, releasing a soluble fragment (sAPP) extracellular which preclude AB formation (1,4). Compelling evidence

Indicates that AB especially the oligomers are toxic to neurons ;excessive generation and accumulation of A peptide sinneuronsis believed to initiate the pathological cascade in AD

Missense mutations in APPP S1, orPS2 gene

Increased Aβ42 production and accumulation

Aβ42 oligomerization and deposition as diffuse plaques

Subtle effects of A βoligomer so synapse's

Microglial and astrocytes' activation (complement factors ,cytokines, etc.)

Progressive synaptic and neurotic injury

Altered neuronal ionic homeostasis; oxidative injury

Altered kinase/phosphatase activities tangles

Widespread neuronal / neuritic dysfunction and cell death with transmitter deficits.

Dementia.[6]

Metformin
Metformin is biguanide and it is the most frequently used oral anti-diabetic drug, which apart from hypoglycaemic activity, improves serum lipid profile positively influences the process of haemostasis,and possesses anti-inflammatory properties. Recently, scientistshav eputthei reffortsin establishing metformin's role in the treatment of neurodegenerative diseases such as AD, amnestic mild cognitive impairment and Parkinson's disease.[7]

Properties of Metformin
White crystalline compound Molecular weight of 165.63.
Metformin HCl is freely soluble in water and is practically in soluble in acetone ether ,and chloroform.

The pKa of metformin is 12.4or1000mg of metforminHCl. Bioavailability of metformin after oral administration has been estimated at approximately50-60%,

Plasma half-life is1.5-4h.
The bioavailability shows some intra-subject, as well as inter-subject variability.

The drug is not bound to plasma proteins Metformin diffuses in to erythrocytes, in a function of time.[10]

CNS Activities of Metformin
Activation of AMPK-dependent pathways in human neural stem cells might be responsible for the neuro protective activity of metformin. Metformin was also found to markedly decease Beta secretase1 (BACE1) protein expressionan dactivityincellcultu remodelsa ndinvivo, therebyreducing BACE1cleavage products and the production ofAβ(β-amyloid). Furthermore there is also some evidence that metformin decreases the activity of acetyl choline esterase (AChE),which is responsible for the degradation of acetylcholine (Ach),a neurotransmitter involved in the process of learning. Inflammatory and anti oxidative properties can not be omitted .Numerous in vitro and in vivo studies have confirmed that metformin ameliorates oxidative damage.[4,5]

AD,T2DM ANDMETFROMIN
Changes in cognition have been reported in type 2 diabetes mellitus (T2DM) patients who have not received a diagnosis of dementia and meta-analyses have found moderate but significant deficits across cognitive domains. T2DM also seems to increase the risk of conversion from mild cognitive impairment to dementia and the conversion from amnestic mild cognitive impairment to AD .Brain imaging studies in T2 DM patients have shown a reduction of whole and regional gray matter volume including hippocampal

volume when compared to non-diabetics. Taken together ,the clinical data mostly shows that T2 DM patients have an increased likelihood of develop ing dementia.The relationship between diabetes and dementia is Further strengthened by reports that reversely, AD patients have an increased risk of developing Type 2 DM or impaired glucose tolerance . The pathological characteristics of AD are as follow: extracellular amyloid plaques consisting of aggregated Aβ, intracellular neurofibrillary tangles (NFTs) comprising hyper phosphorylated tau protein ,and neuronal loss. Aβ develops from consecutive cleavage of the amyloid β precursor protein (APP) by β-site APP cleavage enzyme (BACE1) and theγ-secretase complex/[6] Additionally ,numerous works have provided convincing evidence that AD might be regarded as a metabolic disease in which the brain becomes unable to efficiently utilize glucose for energy production and unable to respond to critical trophic factor signals due to insulin resistance.Metformin does not only decrease the plasma glucose level in severalmechanisms, but is also characterized to beneficially effect serum lipid profiles, reduce inflammatory cell adhesion to endothelium, and exert anti-inflammatory, anti-apoptotic and anti-oxidative properties. For instance ,it was found that metformin decreases interleukin 1β (IL-1β) induced activation of pro inflammatory phosphokinases Akt (proteinkinaseB), p38 (mitogen-activated protein kinase).These effects could be regarded as clinical important for the treatment of brain complications both inT2DM and neurological diseases. On the basis of reviewing scientific literature we can imply that there is a tendency towards the application of metformin in the treatment of Alzheimer's disease(AD).[7]

Parkinsonsdisease

Parkinson's disease (PD) is a common neurodegenerative disease.

Clinical studies have not looked solely at metformin, but rather metformin compared to,or in combination with other oral anti hyperglycemic agents. Taken together a ll the studies look at different medications and are hardly comparable. There is lack of clinical data that suggests a positive effect of metformin on PD risk.Patients with T2 DM receiving sulfonylurea had an increased PD risk compared to those not receiving oral anti-hyperglycemic agents.

Metformin alone or in combination with sulfonylurea had no impact, Suggesting that metformin might rescue the harmful effects of sulfonyl urea.[8]

Other Neurodegenerative Diseases

Amyotrophic Lateral Sclerosis

ALS is a progressive neurodegenerative disease that is characterized by degeneration of the first and second motor neuron resulting in spasticity and muscle atrophy.studies have shown a decreased risk for developing ALS in patients withT2 DM .However,other studies reported no significant effect on ALS risk or progression and even a higher risk of developing ALS in T2 DM in patients below 65 years of age.Nutritional status is negatively associated with ALS severity and hyper caloric nutrition have been suggested as a potential to this diseases.(8)

Huntington Disease

HD is aprogressive neurodegenerative disease that causes choreatic movements,vl psychiatric symptoms, and cognitive decline.The most common form of the disease is of early on set usually diagnosed around 30-40yearsofage.HD is caused by HD patients with T2 DM receiving metformin had better cognitive test results than HD patients without diabetes not taking metformin.This was in stark contrast to the non-HD control group where people with T2 DM taking metformin fared worse in the cognitive test compared to non-diabetic controls.[8,9]

Otheractions

Inflammation

Neuroinflammation is considered a major driving force in the progression of neurodegenerative diseases and the triggering of innate immune mechanisms is emerging as a crucial component in disease pathogenesis. Microglia and other cell types in the brain can be activated in response to misfolded proteins or aberrantly localized nucleic acids.This diverts microgliafrom their physiological and beneficial functions,and leads to their sustained release of pro-inflammatory mediators.Intake of non-steroidal anti-inflammatory drugs (NSAIDs)(8)

Metformin as an AChE Inhibitor

The authors as sessed lipid peroxidation and glutathione levels parameters of oxidative stress and choline esterase (ChE) activity as amarker of cholinergic function.

Metforminas an Antioxidant studies have documented that Aβ may interact with mitochondrial proteins, and later on, disrupt the electron transport chain, promote mitochondrial dysfunction and the generation of ROS.It has also been reported that oxidative stress may enhance hyper phosphorylation.

Metformin: Mechanism of Action In Neuro Degenerative Diseases

The invivo studies conducted so far,regarding the effect of metformin have generated conflicting results.Besides the large differences in study design, these outcomes are probably also due to the many biological pathways influenced by metformin.the biological signaling pathways and biological mechanisms that are the most relevant for metformin's potential as a therapy in neuro degenerative disease.[10]

Central Metabolism and Signaling

Central metabolism is tied to the over arching cell signaling pathways involved in proliferation,stress and survival,which are heavily implicated in human diseases including cancer and neuro degeneration.Metformin acts on central metabolism and several major signaling pathways including energy sensing (glucose metabolism and AMPK signaling), mTOR signaling ,and inflammatory signaling and Mitochondrial signaling.[11]

Energy Sensing and Metabolism

The brain constitutes only 2% of the total body mass, but it is one of the main energy-demanding organs in the human body utilizing around 20% of total energy expenditure.Brain cells incorporate.

(i) The neurons (70-80%of brainenergy expenditure)

(ii) Glialcells, comprising oligodendrocytes astrocytes and microglia (accounting for the remaining 20-30% of energy expenditure).The high energy demand of neurons is one of several factors partially explaining the selective vulnerability of certain neuronal sub type in neurodegenerative diseases. Energy metabolism has long since been thought to play a role in the etiology of neurodegenerative diseases and here we will briefly mention some of the related signaling pathways and biological mechanisms that are relevant for metformin's therapeutic potential in neuro degeneration.[10]

AMPK signaling

AMPK is an evolutionarily conserved sens or of cellular energy status.AMPK is activated by increasing AMP levels in conditions of energy deprivation and the enzyme consequently inhibits energy consumption and stimulates catabolic pathways.Activation of AMPK has a wide range of effects, including inhibition of mTor and PI3K-Akt signaling pathways Dysregulation of AMPK is associated with insulin resistance and T2 DM and neuro inflammation. AMPK signaling plays a major role in AD disease progression since AMPK has been shown to regulate both Aβ generation and tau phosphorylation.Metformin inhibits complex I of the electron transport chain needed for mitochondrial respiration,there by leading to an energy deficit and indirectly activating the AMPK pathway.metformin administration,explaining many of the known effects of the drug.

However, in the context of AD especially, more studies are needed to understand the complex role of AMPK signaling and the action of metformin.A study conducted in human neuronal stem cells proposed that activation of AMPK via metformin is neuroprotective against Aβ. invitro studies showed that metformin is able to reduce tauphosphorylation via mTOR/PP2A (Protein phosphates 2A) signaling and that it can reduce molecular pathologies associated with AD.[11]

Glucose Metabolism

Metformin can act in these pathways by slowing oxidative phosphorylation via inhibition of complex I in mitochondria and by inhibiting gluconeogenesis, having the effect of further aid in neurons to reduce their oxidative burden by minimalizing NADH utilization.[8,12]

Insulin Signaling

Insulin plays an important role in the brain.It is used as a hormonal signal to control body weight, food uptake, and metabolic homeo stasis. Insulin has also been shown to influence expression of dopamine receptors and concentration of dopamine. Disturbances in insulin signaling have been implicated in several neurodegenerative diseases including AD ,PD, and HD. Insulin is secreted in response to high blood sugar and acts indifferent organs including the brain. Activation of the Phospho inositide-3-kinase (PI3K)—Akt pathway via insulin receptor activation and insulin receptor substrates plays a central role in the metabolic actions of insulin.Akt activationregulatesproteinssuchasmTOR,FOXO,andBAD.Overall,Akt has over 100 known substrates and has diverse effects on cellular growth, cell proliferation, glucose uptake, protein synthesis, glycogen synthesis.[13]

Metformin lowers blood glucose levels through inhibition gluconeogenesis in the liver via AMPK.AMPK inhibits PI3K/Akt signaling, the crucial pathway downstream of the insulin and IGF1 receptors.Metformin has also been shown to act on insulin signaling independently of AMPK. Metformin is reported to down regulate expression of insulin and IGF-1 receptors and reduce phosphorylation of insulin receptors.[14,15]

mTOR Signalling

mTOR signalling is a highly conserved and central signalling pathway integrating upstream signals such as nutrient and redox status and then controlling downstream processes such as cellular growth, motility, survival, and death.The mTOR pathway is crucial for regulating mitochondrial biogenesis and autophagy,two processes that are defective in many neurodegenerative diseases.[15]

mTOR is a serine/threonine protein kinase, composed of the protein complexes mTOR C1 and mTORC2.mTOR signaling is targeted by the PI3K/Akt pathway,the key insulin signaling pathway..Both PTEN and AMPK suppress mTor signaling and rapamycin is a well-studied inhibitor of mTORC1.Although mTor signaling influences many downstream events, the most important mechanism of action is through the phosphorylation and activation of S6K1 and 4E-BP1and subsequent control of RNA translation.Interestingly,deficiency in mTor signaling has been implicated with insulin resistance and

diabetes.Nutrient dependent stimulation of S6K1 can induce insulin resistance and S6K1 deficiency protects against high fat diet-induced insulin resistance.

Nevertheless,the mTOR pathway links several biological pathway underlying neurodegenerative diseases and therefore the ability of metformin to inhibit this signaling cascade endorses the argument that more mechanistic work using metformin and it's inclusion in clinical trials should be positively considered.[16,17]

CONCLUSION

Alzheimer's disease (AD) is the most common form of senile dementia, affecting 10% of individual solder than 65andnearly 50% of those older than85. The pathophysiology of AD is associated with a variety of factors, Including the extracellular deposition of b-amyloid (Ab) plaques, Accumulation of intracellular neuro fibrillary tangles, oxidative neuronal damage, and inflammatory cascade. Although great advances have been made in the last decades to understand the underlying genetic and biological cause of these diseases, only some symptomatic treatments are available. Metformin has long since been used to treat Type 2 Diabetes and has been shown to be beneficial in several other conditions. Metformin is well-tested in vitro and in vivo and an approved compound that targets diverse pathways including mitochondrial energy production and insulin signalling.

There is growing evidence for the benefits of metformin to counteract age-related diseases such as cancer, cardio vascular disease, and neurodegenerative diseases. It shows how metformin is able to balance survival and death signaling in cells through pathways that are commonly associated with neurodegenerative diseases.In healthy neurons,these over arching signals keep energy metabolism,oxidative stress,and proteo stasis in check, avoiding the dysfunction and neuronal death that defines neurodegenerative disease.The biological mechanisms involved and the relevance of neuronal vulnerability and potential difficulties for future trials and development of therapies. There is potentia l that metformin could be beneficial in the task of counteracting aging and clinical studies imply that metformin may have positive effects on cognition in T2 DM patients. A better understanding of how metformin works will help researchers in the neuro degeneration field to successfully design future research and trials. Upcoming studies such as TAME will help in this respect.

The anti-aging effects of metformin could be summarized by its ability to interfere with the multi stage process of energy production without producing damaging amounts of ROS.This action alone could be seen as neuroprotective and metformin may further protect by activating other biological pathways. For example, slowing mitochondrial energy production canal so trigger a cascade of signaling events in the liver that result in reduced glucose and insulin.

The key role of insulin in nutrient sensing which balances growth andproliferation with life-extending conservation, makes metformin an interesting drug. The field of aging research is growing and in vivo and in vitro aging models are advancing.Probably due to the complexity of metformin action,this drug will not likely serve as a potential treatment for neuro degenerative diseases on the current stage because much more work is needed to understand the role of aging in different neurodegenerative disease forms. The greatest value of metformin today might lie in it's potential to help decipher those mechanisms underlying neuro degeneration.

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