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SUMMARY

CHAMP1 gene encodes a zinc finger protein that regulates kinetochore/microtubule attachment and maintains accurate chromosomal segregation during mitosis.

Loss-of-function CHAMP1 variants result in abnormal cell cycle signaling among other important pathways, as captured by transcriptomic analyses. Transcriptomic analyses of the CHAMP1 patients' fibroblasts have identified several genes that are either up or downregulated as a result of the CHAMP1 variant. We used mediKanren – our biomedical reasoner tool - to query what chemicals and/or drugs may reverse the abnormal gene expressions found in the fibroblast transcriptomic data. Our analyses show that several compounds might be useful to reverse the downstream molecular effects of the CHAMP1 variants that may underlie the symptoms of his disorder.

Among other drugs/compounds, metformin was prioritized based on the number of potentially affected genes together with safety and other practical concerns to potentially reverse the expected molecular impact of CHAMP1 variants.

THERAPEUTIC RATIONALE

Metformin, the most common antidiabetic medication, is predicted to reverse several genes' expression in CHAMP1 patient-derived fibroblasts. It also has been shown to improve cognitive function in children with learning disabilities and cognitive impairments.[1]

Metformin exerts its potent antihyperglycemic effects via inhibition of mitochondrial complex I activity, which decreases ATP production and subsequently leads to the activation of AMPK and inhibition of mTOR signaling. These events eventually decrease hepatic gluconeogenesis, causing an increase in peripheral glucose uptake and insulin sensitivity (Figure 2). Besides diabetes and cancer, dysregulation in mTOR signaling has also been observed in several neurological disorders such as autism spectrum disorder, fragile X syndrome, epilepsy, Alzheimer's disease, Parkinson's disease, Huntington's disease, major depressive disorder, and schizophrenia.[2]

Many studies have elucidated several distinct mechanisms by which metformin disrupts mTOR pathway activity and exerts its neuroprotective and neurogenesis effects, raising a strong interest in repurposing this safe and effective anti-diabetic drug for neurodevelopmental and neurodegenerative disorders (Figure 1).[3] In cell studies, metformin protected primary cortical neurons from apoptosis,[4] promoted self-renewal and differentiation of neural precursor cells[5] and supported neuronal differentiation and neurite growth in human bone marrow-mesenchymal stem cells.[6] In animal studies, metformin also protected the murine neonatal brain from

hypoxia-ischemia injury,[7] enhanced spatial memory,[5,8] and increased life span in mice.[9] In humans, metformin was demonstrated to be safe and effective in metabolic regulation in patients with schizophrenia,[10] autism spectrum disorder [11,12] as well as improving cognitive functions in several other disease groups. [3,13-18] For instance, as the first line of treatment for diabetes, metformin usage was strongly associated with slower cognitive decline in older adults [13-15] In younger populations, metformin also promoted brain repair in pediatric brain tumor patients who received radiation therapy[1] and improved cognitive functions in individuals with fragile X syndrome – the most prevalent form of inherited intellectual disability.[3,17-18]

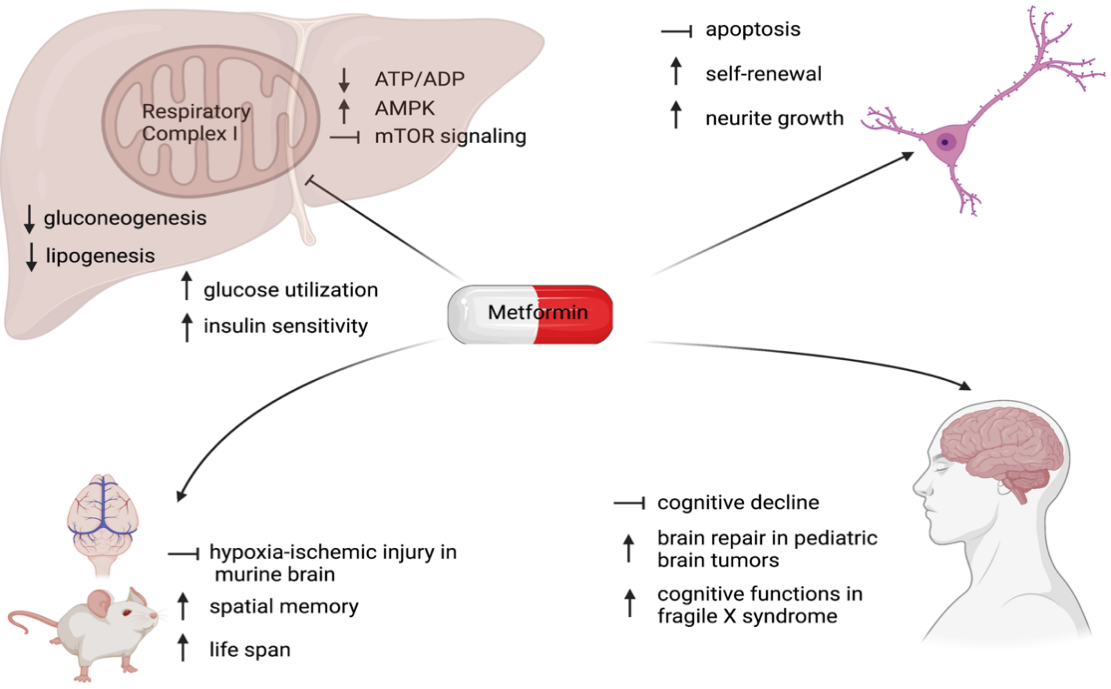

Figure 1: Metformin mechanism of actions and evidence that supports repurposing metformin for neurodevelopmental disorders

Besides neuroprotective effects, metformin has also been demonstrated to have anti-seizure properties,[19] which may provide additional favorable therapeutic effects for the participant. Several animal studies have established the anti-seizure effects of this mediation.[20-24] In humans, a recent clinical trial on Tuberous Sclerosis Complex (TSC) in the UK found that metformin reduced the frequency of seizures by ~40% along with a 21% reduction in the size of brain tumors.[25]

Collectively, these pieces of evidence strongly support the rationale to repurpose metformin, an antidiabetic medication, to improve cognitive functions and manage seizures in this participant.

Known Unknowns

We acknowledge that the majority of the articles used in our analyses are preclinical and therefore the effects in humans may be different. However, all therapeutic options suggested are either supplements or FDA-approved as safe for use in humans.

We do want to note that metformin is currently not indicated for improving cognitive functions nor managing seizures in patients with neurodevelopmental disorders.

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