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Neuroprotective Effect of Metformin

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We read the article "Predictors of Metformin Side Effects in Patients with Newly Diagnosed Type 2 Diabetes Mellitus" in the esteemed "Ibnosina Journal of Medicine and Biomedical Sciences" with great interest. Alibrahim et al assessed possible variables that may influence the development of metformin side effects. The most common side effect of metformin was diarrhea. The authors found that the female sex, high fasting blood glucose, and increased body mass index were significantly associated with the discontinuation of metformin. Interestingly, a rapid dose escalation was related to a higher frequency of adverse events.[1]

Metformin is a biguanide antihyperglycemic agent known for its ability to reduce glucose production and improve insulin sensitivity. In 1922, Emil Werner and James Bell first described metformin as an N,N-dimethylguanidine product. However, there are some side effects associated with metformin. Recent studies have shown that this biguanide agent can mediate neuroprotection.[2] Herein, we would like to discuss the current literature regarding the neuroprotective effects of metformin (►**Fig. 1**).

The occurrence of acute stroke is closely related to the inflammatory state and oxidative stress. Cerebral ischemia may be associated with dysregulation of the adenosine monophosphate-activated protein kinase pathway. In rat models, metformin revealed a reduction in neuronal apoptosis and area of cerebral infarction. Zhao et al evaluated the effect of metformin on neurological function and oxidative stress in individuals with type 2 diabetes mellitus during the acute phase of stroke. The authors found that metformin compared with the insulin group significantly improved neurological function scores in Mini-Mental State Examination ($t = 8.11$), National Institutes of Health Stroke Scale ($t = 6.52$), and Activities of Daily Living ($t = 8.38$). Also, a significant improvement was observed in inflammatory biomarkers, such as glutathione ($t = 7.32$), malondialdehyde ($t = 5.72$), and superoxide dismutase ($t = 7.24$).[3]

Complex I (NADH-ubiquinone oxidoreductase) deficiency is childhood's most frequent mitochondrial disorder. NADH-ubiquinone oxidoreductase iron-sulfur protein 3 (NDUFS3) is a subunit of complex I. Mutation of NDUFS3 can lead to complex I deficiency. Peralta et al studied the effect of metformin in neuron-specific NDUFS3 conditional knockout mouse models. They observed that the administration of metformin to these mice delayed the onset of neurological symptoms but not neuronal loss.[4] Peralta et al hypothesized that the improvement was probably associated with increased glucose uptake by neuronal cells due to metformin administration.

Zemgulyte et al assessed the neuroprotective effect of metformin treatment after permanent middle cerebral artery occlusion in rat models. The authors found that metformin can reduce neurological disabilities and reduce infarct size within 120 hours of a stroke. Also, if started within the first 2 days of stroke, metformin can prevent neuronal cell loss in the cortex and reduce the total number of activated microglia. Moreover, treatment with metformin further increased interleukin-10 in the cerebral cortex and striatum of the ischemic hemisphere.[5]

Authors' Contribution

All the authors contirbuted equally.

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Conflict of Interest

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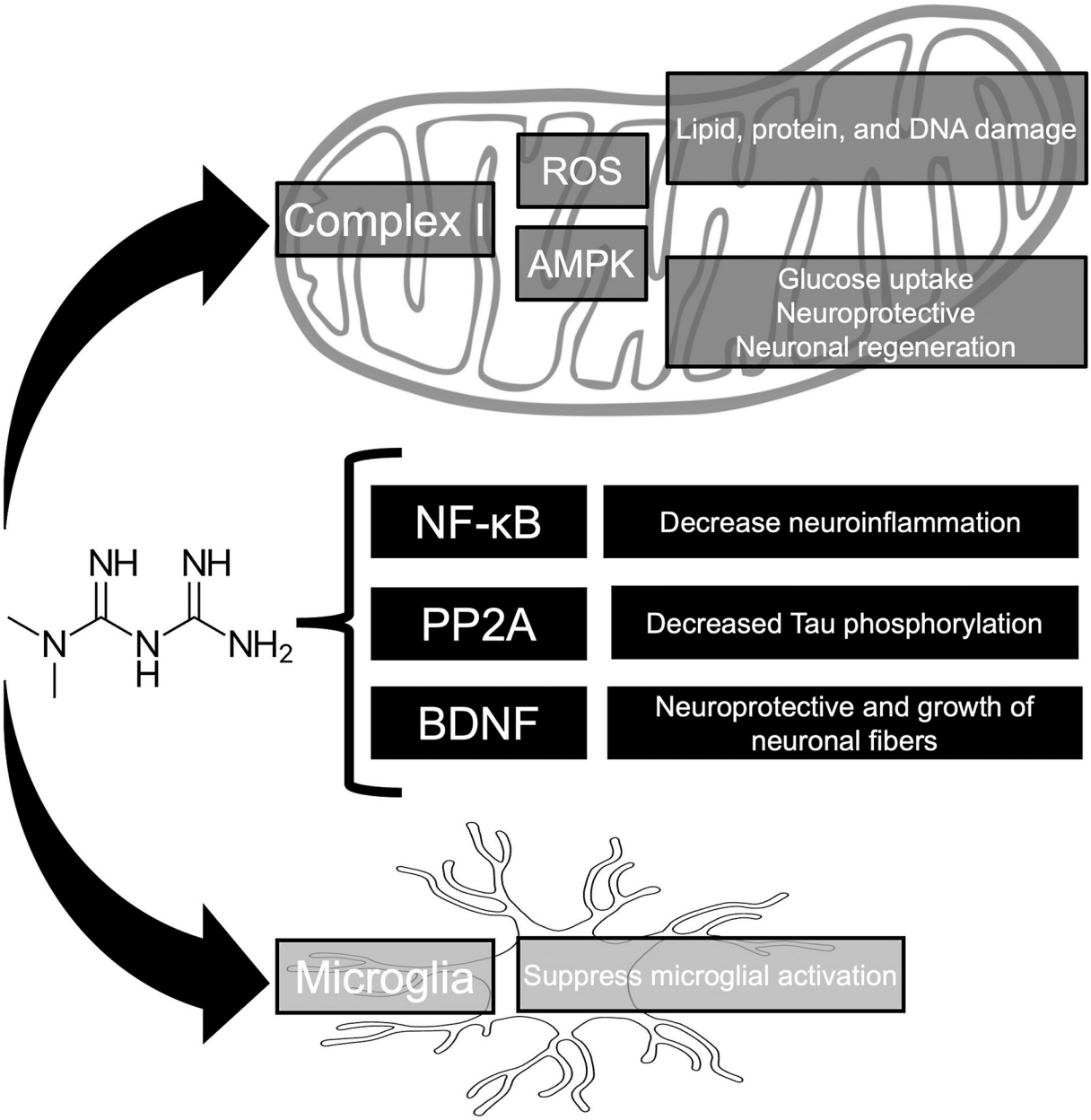

Fig. 1 Neuroprotective effect of metformin. AMPK, adenosine monophosphate-activated protein kinase; BDNF, brain-derived neurotrophic factor; DNA, deoxyribonucleic acid; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PP2A, protein phosphatase 2A; ROS, reactive oxygen species.

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