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Pharma Europe 2020 : Clozapine attenuated mitochondrial dysfunction, inflammatory gene expression, and behavioural abnormalities in an animal model of schizophrenia - Mir-Jamal Hosseini - Tehran University of Medical Sciences

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ABSTRACT

Objectives: Beyond abnormalities in neurotransmitter hypothesis, recent evidence suggests that mitochondrial dysfunction and impaired immune system contribute to the pathophysiology of schizophrenia. Prefrontal cortex (PFC) undergoes maturation and development during adolescence as a critical time window, during which brain is vulnerable to environmental adversities and is prone to the development of psychiatric disorders such as schizophrenia. Methods: Applying eight weeks of post weaning social isolation stress (PWSI) to rats, as an animal model of schizophrenia, we evaluated the effects of PWSI on the mitochondrial function and expression of immune-inflammatory genes in the PFC of normal and stressed rats and then, each group were divided into treatment (clozapine; CLZ, 2.5 mg/kg/day for 28 days) and non-treatment groups. Results: Our data showed that PWSI provoked schizophrenic-like behaviors in rats and induced mitochondrial dysfunction and upregulation of genes associated with innate immunity in the PFC. Chronic treatment with CLZ attenuated the effects of PWSI on behavioral abnormalities, mitochondrial dysfunction as well as immune-inflammatory responses in the PFC of rats. Conclusions: These results may advance our understanding about the mechanism of action of CLZ that targets mitochondrial dysfunction and immune-inflammatory responses as factors involved in the pathophysiology of schizophrenia. The complexity of schizophrenia may help explain why there are misconceptions about the disease. Schizophrenia does not mean split personality or multiple-personality. Most people with schizophrenia are not dangerous or violent. They also are not homeless nor do they live in hospitals. Most people with schizophrenia live with family, in group homes or on their own. Research has shown that schizophrenia affects men and women about equally but may have an earlier onset in males. Rates are similar around the world. People with schizophrenia are more likely to die younger than the general population, in part because of high rates of co-occurring medical conditions, such as heart disease and diabetes.

Key words: Schizophrenia; Clozapine; Mitochondria; inflammation; Social isolation stress, Adolescence.

Introduction:

Clozapine is an atypical antipsychotic that is highly efficacious for the treatment of schizophrenia. However, along with most atypical antipsychotics, clozapine has been found to cause DIMS, giving rise to adverse metabolic side effects such as obesity and increased diabetes risk The underlying biological causes of clozapine-associated DIMS are unknown. There is a growing consensus in the obesity and diabetes fields that understanding the mechanisms responsible for the adverse metabolic effects of atypical antipsychotics may shed an important light on the origin of MetS, and this is the rationale for using this model in the current study. There are three interrelated hypotheses that have been proposed to explain antipsychotic-induced metabolic side effects. First, these drugs negatively affect the proper functioning of mitochondria Specifically, these drugs may alter the function of key metabolic enzymes and thus negatively affect carbon metabolism and/or electron transport during oxidative phosphorylation. Clozapine has been shown to market the oxidation of mitochondrial proteins involved in energy metabolism in neuroblastoma cells and in lymphoblastoid cells of schizophrenia patients Oxidized proteins included enzymes important in carbon metabolism such as pyruvate kinase and mitochondrial malate dehydrogenase. Analyses of rat or mice brains have shown that clozapine alters mitochondrial function, energy metabolism, and expression of mitochondrial proteins belonging to the electron transport chain and organic process pathway, such as succinate dehydrogenase and cytochrome oxidase.

Mitochondria play a critical role in regulating cellular functions including bioenergetics, calcium homeostasis, redox Signalling, and apoptotic cell death. Mitochondria also are essential to several aspects of neurodevelopment and neuronal functions. However, mitochondrial impairment may affect bioenergetics in the developing brain and alter critical neuronal processes leading to neurodevelopmental abnormalities. Schizophrenia is one of the chronic and severe neuropsychiatric disorders of neurodevelopmental origin. Immuno-inflammatory pathway is one among the widely appreciated mechanisms that has consistently been implicated within the neurodevelopmental origin of schizophrenia. However, the source of inflammation and the underlying neurobiological mechanisms leading to

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schizophrenia are yet to be fully ascertained. Recent understanding reveals that perturbation of mitochondrial network dynamics might cause various Nervous System disorders with inflammatory pathologies. Mitochondrial deficit, altered redox balance and chronic low-grade inflammation are evident in schizophrenia. It is hypothesized that oxidative/nitro active stress responses thanks to mitochondrial dysfunctions might activate immuno-inflammatory pathways and subsequently cause neuro progressive changes in schizophrenia. Herein, we Summarise the present understanding of molecular links between mitochondrial dysfunctions and pathogenesis of schizophrenia supported evidence from genomics, proteomics and imaging studies, which together support a role for mitochondrial impairment within the pathogenetic pathways of schizophrenia.

In addition, alterations in electron transport were demonstrated in peripheral blood cells of patients taking atypical antipsychotics . Second, these drugs may cause increased oxidative stress in cells and tissues . In addition to direct protein oxidation, antipsychotic treatment has been related to increased production of reactive oxygen species (ROS) and antioxidant proteins. In a study of patients undergoing long-term clozapine treatment, there have been elevated levels of the antioxidant enzyme SOD in red blood cells . Further evidence of clozapine-induced production of reactive oxygen species (ROS) was demonstrated in rat whole blood and rat brain . Third, these drugs promote inflammation There is evidence to suggest that clozapine influences the assembly of several cytokines and/or cytokine receptors that modulate immunological Responses . In stimulated blood from healthy donors, clozapine treatment increased levels of IL-4 and IL-17. In a study which administered clozapine to schizophrenia patients over a six week period, plasma levels of cytokines, including TNF-α, sTNFR-1, sTNFR-2, IL-6, and sIL-2R, were found to extend significantly over the treatment time . Lastly, it is important to note the interplay between these three proposed mechanisms. Mitochondria that are damaged are known to supply increased levels of ROS and initiate inflammation; oxidative stress itself can damage mitochondria and promote an inflammatory response Similarly, a pro-inflammatory state contributes to increased ROS production and may negatively affect mitochondria function, either directly, or through oxidative stress . Schizophrenia is a chronic brain disorder that affects less than one percent of the U.S. population. When schizophrenia is active, symptoms can include delusions, hallucinations, trouble with thinking and concentration, and lack of motivation. However, with treatment, most symptoms of schizophrenia will greatly improve.

Biography :

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