

Mitochondrial dysfunction of Clozapine attenuation, inflammatory gene expression, and behavioural abnormalities in an animal model of schizophrenia- Hosseini Mir-Jamal - Tehran University of Medical Sciences

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ABSTRACT

Beyond abnormalities in neurotransmitter hypothesis, recent evidence suggests that mitochondrial dysfunction and impaired 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 susceptible to environmental adversities and is susceptible to the event 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 consequences of PWSI on the mitochondrial function and expression of immune-inflammatory genes within the PFC of normal and stressed rats 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 consequences of PWSI on behavioral abnormalities, mitochondrial dysfunction also as immune-inflammatory responses within 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 within 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 multiplepersonality. Most people with schizophrenia aren't dangerous or violent. They are also not homeless nor do they sleep in hospitals. Most people with schizophrenia accept family, in group homes or on their own. Research has shown that schizophrenia affects men and ladies 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. Clozapine is an atypical antipsychotic that's 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 within the obesity and diabetes fields that understanding the mechanisms liable for the adverse metabolic effects of atypical antipsychotics may shed a crucial light on the origin of MetS, and this is often the rationale for using this model within 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 right 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 like 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 biological 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 necrobiosis . Mitochondria are also essential to many aspects of neurodevelopment and neuronal functions. However, mitochondrial impairment may affect bioenergetics within the developing brain and alter critical neuronal processes resulting in neurodevelopmental abnormalities. Schizophrenia is one among 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 therefore the underlying neurobiological mechanisms resulting in 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 because of mitochondrial dysfunctions might activate immunoinflammatory pathways and subsequently cause neuro progressive changes in schizophrenia. Herein, we Summarise this understanding of molecular links between mitochondrial dysfunctions and pathogenesis of schizophrenia supported evidence from genomics, proteomics and imaging studies, which together support a task for mitochondrial impairment within the pathogenetic pathways of schizophrenia.

Keywords: Schizophrenia; Clozapine; Mitochondria; inflammation; Social isolation stress, Adolescence