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Conceivable Mechanisms of Clozapine Propagated Dyslipidemia- A Short Review

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Review Article

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ABSTRACT

Clozapine is the most effective drug for the treatment of refractory schizophrenia, showing a good response in the treatment of patients with resistant schizophrenia, especially reducing violent, aggressive, and suicidal tendencies. However, treatment with clozapine has been associated with hyperlipidemia especially high triglycerides, obesity, diabetes, and cardiovascular disease. Elevated level of lipids has a direct impact on the improvement of symptoms in schizophrenics treated with clozapine. Although the mechanism is not clear, there is a possibility of serum lipids playing a major part in enhancing clozapine's therapeutic activity. The effect of clozapine on phospholipids might indicate that this rise is related to its therapeutic benefit as well. Increase in fatty acids accompanied by a sharp rise in triglycerides may alsocontribute, pointing towards the possible involvement of lipases which are involved in the storage and release of fatty acids and triglycerides in the adipose tissue. An increase in hepatic lipid synthesis can be one other cause for hyperlipidaemia, leading to weight gain after a long term therapy. Lipogenesis and myelin synthesis could also become targets in schizophrenia since myelination and synaptogenesis is essential in the central nervous system. Hence a focus is put on the upregulation of several genes involved in cholesterol and fatty acid biosynthesis, which are proven to be controlled by Sterol Regulating Element Binding Protein transcription factors (SREBP). The antipsychotic drug Clozapine activates this SREBP system. This activation increases lipogenesis which could be one of the mechanisms of action, which in turn could explain the metabolic side effects produced by clozapine.

INTRODUCTION

Antipsychotics have always been the pillars of treatment in mental illnesses especially in case of schizophrenia. But it has been widely demonstrated that around 60% of patients with schizophrenia do not show the required response to conventional treatments. It has been proven that clozapine is more effective than any other antipsychotics in the treatment of drug resistant schizophrenic patients. Since the crucial study of Kane et al, clozapine has been carried on as the most favorable drug in treatment resistant schizophrenia despite the risk of agranulocytosis which is the main adverse effect, other adverse effects being tremors, akathisia. Clozapine is thus the drug of choice when the patients show less to negligible response to standard antipsychotic therapies [1].

Amongst the various antipsychotics, ziprasidone, risperidone and aripiprazole appear to be associated with a relatively low risk for hyperlipidemia, whereas quetiapine, olanzapine, and clozapine are associated with a relatively high risk for hyperlipidemia. There has been a high prevalence of metabolic syndrome in chronic schizophrenics. However, clinical

experience has reported that only some of these drugs have the potential to induce considerable weight gain. Possible underlying causes of lipid dysregulation include weight gain, dietary changes, and glucose intolerance, medications, sedentary lifestyle, etc. Weight gain induced by clozapine is not considered harmful or life threatening if controlled properly. Couple of reasons ranging from genetic to environmental are responsible for the risk of cardio vascular diseases in schizophrenic patients [2].

All antipsychotics show their action through inhibition of dopamine D_2 receptors in the mesolimbic frontal brain regions. Clozapine works by blocking receptors in the brain for several neurotransmitters. Clozapine acts as an antagonist of dopamine (D_2 and D_4) and serotonin ($5HT_2$ and $5HT_3$) receptors, as well as adrenergic, cholinergic, and Histamine (H_1) receptors. Adenyl cyclase, an enzyme which mediates the effects of a number of hormones on their target tissues, is positively linked with 5HT receptors especially in the CNS. The moderate D_2 antagonism is a means for enhanced therapeutic efficacy against psychosis as is seen in the case of clozapine. It has been observed that clozapine has a higher affinity for H_1 receptors, which proves the involvement of these receptors in weight gain. There is a strong link between the defective N-Methyl D-Aspartate receptors (NMDA) and schizophrenia symptoms. NMDA receptors control the synapses and are linked to memory and learning abilities. Naturally occurring agents could bring down the positive and negative symptoms seen in schizophrenia [3].

Clozapine is linked to a variety of unfavorable outcomes. The common ones are metabolic disturbances in glucose, insulin, lipids, and an increase in weight gain, which collectively is referred to as metabolic syndrome. A study done on OPD patients treated with clozapine noted about 80% to be overweight; 58% met the standard scale for metabolic syndrome, parallelly showing very high rates of rise in blood pressure, sugar and lipids. The existence of metabolic abnormalities in an individual exacerbates the risk for morbidity and increases the mortality rate. Persons with chronic and severe mental illnesses like schizophrenia are prone to develop metabolic abnormalities. Interestingly, people with mental disorders have been a target for studying the prevalence of obesity related diabetes and lipid abnormalities. Atypical antipsychotics, when combined with mood stabilizers have a better efficacy and most are considered for treatment due to their less extrapyramidal side effects. Second generation antipsychotics are known to aggravate the characteristics of the metabolic syndrome like those related to glucose and lipids, but the mechanisms by which they increase weight and produce metabolic disturbances are not clear. A study done by Goran, et al., showed a steady elevation in free fatty acids and glucose in serum, followed by accumulation of lipids in the liver almost after 12-24 hrs., proving biphasic patterns of increased gene expression involved in glucogenesis and lipogenesis both in the liver and white adipose tissue depots. This marked elevation of hepatic lipids was accompanied by immediate drug-induced transcriptional activation of SREBP controlled lipogenic genes in the liver for clozapine. Atypical antipsychotics, in particular clozapine, are capable of increasing body weight and adiposity by increasing adipose tissue lipolysis (*i.e.,* triglyceride hydrolysis). Although the use of second generation antipsychotics is thus clearly associated with increased risk to develop metabolic syndrome, specific factors that increase this risk have remained largely elusive [4].

In a particular study, the triglyceride levels were found to be double after chronic treatment with clozapine. Moreover, cholesterol levels were increased by at least 10% in the same study group. However, cases are rare in the literature that shows sudden development of hypertriglyceridemia without associated obesity or glucose abnormality. There is a plethora of hypotheses to explain the metabolic abnormalities like weight gain, dyslipidemia, increased insulin resistance associated with clozapine medication. Usually, patients with schizophrenia are predisposed to obesity due to positive and negative symptoms that are the major features of this mental illness, and the overall sedentary lifestyle can add up to this obesity. Furthermore, antipsychotic drugs result in increased appetite and excess food intake, possibly mediated through histamine H_1 and serotonin $5HT_2C$ receptor antagonists in the hypothalamus as well as alterations in hypothalamic fatty acid metabolism and neuropeptide expression. Other possible mechanisms by which clozapine produces metabolic abnormalities involve suppression of insulin release, insulin resistance, or impairment of glucose utilization. All the above are plausible mechanisms explain metabolic complications of antipsychotics over a period. This review is taken to list out the possible mechanisms that hold good for clozapine-induced lipid alterations. Several studies have pointed to certain abnormalities in cell membranes and brain lipids that compromise the structural integrity and functional properties of neurons in patients with mental disorders [5].

LITERATURE REVIEW

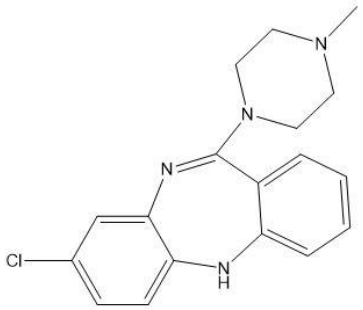
A review of 50 articles identified through search in Pubmed, Google scholar was done using keywords for search like clozapine, schizophrenia, metabolic syndrome, hyperlipidaemia, antipsychotics, adipose tissue, lipid accumulation, SREBP gene etc. Among 50 articles, 20 articles were taken for further evaluation to assess the full text of these articles for potential eligibility especially studies who reported associations of clozapine/antipsychotics with lipid abnormalities and weight gain explaining mechanism of action were most considered [6].

Pharmacology of clozapine

It is an antipsychotic drug especially used in treatment resistant schizophrenia and to decrease suicidal risk in schizophrenic patients (Figure 1). It is a tricyclic dibenzodiazepine, soluble in water and acetone, highly soluble in

chloroform. Its chemical formula is $C_{18}H_{19}ClN_4$[7].

Figure 1. Structure of clozapine.



Clozapine was synthesized in 1956 by Wander AG. In 1975, 16 cases of agranulocytosis leading to 8 deaths in clozapine-related patients were reported, and so strict monitoring during the first 18 weeks of treatment was proposed. The role of clozapine in treatment-resistant schizophrenia was established by the landmark clozaril collaborative study group that showed marked benefits of clozapine, it took 14 years to reveal the results of the pivotal US clozaril Study. Thus, the important role of clozapine in clinical practice was discovered. It was quite later following a study in 1990, the US food and drug administration approved clozapine use. Clozapine may cause serious and potentially fatal adverse effects including neutropenia, orthostatic hypotension, slow heart rate, fainting, seizures, myocarditis, and risk of death. Common adverse effects include constipation, sedation, increased blood sugar, weight gain, etc. Impaired glucose metabolism and obesity are constituents of the metabolic syndrome and may increase the risk of cardiovascular diseases. Data suggests that clozapine may be more likely to cause adverse metabolic effects than some of the other atypical antipsychotics. Clozapine's superiority is not confined to a particular aspect or dimension of psychopathologic characteristics (e.g. hallucinations, delusions, or suspiciousness) but involve all the major psychotic signs and symptoms associated with the patients, including negative items as blunted affect, emotional withdrawal, apathy, and disorientation [8-10].

Pharmacokinetics

Clozapine is very well absorbed, metabolized in the liver by cytochrome P450 system (primarily CYP1A2) and excreted both in the urine and stools. The first step of the metabolism pathway reduces the bioavailability of clozapine to almost 60 to 70 percent of the administered dosage. Food does not have much effect on the availability of clozapine in the body. The half-life of clozapine is approximately 8-14 hours but may vary from person to person [11].

Pharmacodynamics

Clozapine loosely binds to dopamine receptors especially D_2 transiently. Conventional antipsychotic medications usually induce catalepsies, unlike clozapine which does not; it is this unique quality that may explain it's little or negligible chance of causing motor abnormalities as compared to other antipsychotics like haloperidol that tightly binds to D2 receptors. It is also known that clozapine binds to D_1, D_3, D_4, and D_5 receptors but the connections of such binding activity are not clear [12].

Clozapine and weight gain

It has been reported that among the atypical antipsychotics, the drugs clozapine and olanzapine are more likely to induce weight gain, and the prevalence of obesity is 64% in adults who are on clozapine, 56% in adults who are on other atypical drugs when compared to 28% in the non-medicated group of adults. This could be explained by a greater orexigenic effect of the antipsychotic drugs in adolescents. The mechanism responsible for clozapine induced weight gain at a molecular level remains unclear. One of the proposed mechanisms is the ability to induce hyperphagia by acting as antagonists of neurotransmitter specifically histamine, serotonin, or dopamine receptors in the CNS. Antipsychotic drugs usually interact with the receptors and initiate the signal transduction pathway which can be a factor responsible for weight gain. Again we must consider that obesity may be an outcome of amalgamate action of an antipsychotic compound on numerous receptors at the same time. The regulation of appetite and food ingestion is caused by the action of hypothalamic neurotransmitters and neuropeptides. On the contrary, the neurotransmitter serotonin (5-HT) intensifies satiety and regulates the intake of food, and serotonin 2C (5-HT_2C) receptors avert satiety due to its antagonism. Proposed mechanisms also include 5-HT_2c antagonism, hyperprolactinemia, elevated serum leptin levels (leading to leptin desensitization), and H1 antagonism. Goran, et al. Demonstrated how the serum glucose, free fatty acids, and glucagon increased rapidly with an acute injection of clozapine or even olanzapine for that matter, which eventually led to the accumulation of lipids in the liver. This observation was seen to be independent of food intake and gain of weight. And so, it would be correct to say that chances of weight gain could be related to a clinical reaction. Cai, et al. observed noted elevations in the metabolic parameters caused by Atypical Anti-Psychotic Drugs (AAPD) that occurred even before the visible weight gain, providing profane associations between antipsychotic drugs and metabolic outcomes [13].

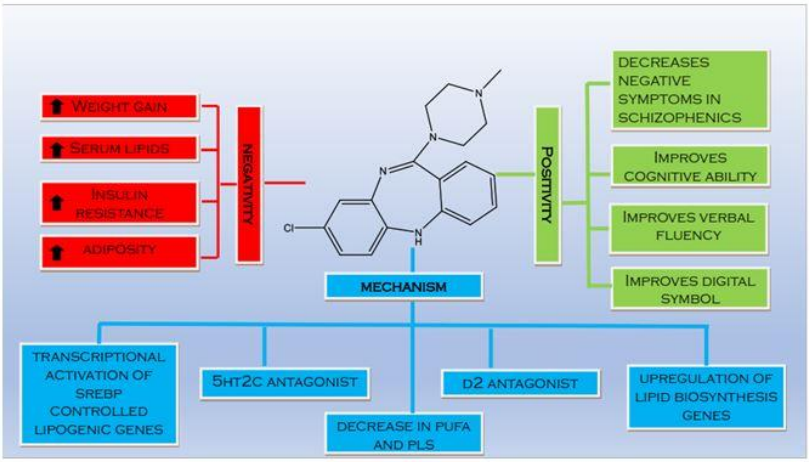
Additionally, some findings suggest that some antipsychotic-mediated metabolic abnormalities occur without the involvement of weight gain. Some authors believe that intra individual variability is a natural existence and varying concentrations of serum lipids could be attributed to this. It is a known fact that lipid concentrations vary considerably between individuals over moderately shorter periods. Intrinsic factors (*i.e.,* hormonal regulation), extrinsic factors (*i.e.* diet), and biological factors are some of the ascribing variables. Intrinsic factors are the main events that are responsible for changes in lipid levels due to their biosynthesis in the body and usage by the tissues, which are in turn regulated by genes and also their interaction with other extrinsic factors. In one study, after giving a single intraperitoneal injection of the drug clozapine, the mice showed some transcriptional effects in the liver which were mediated through genes that directly controlled transcription factors like SREBP transcription factor, liver X receptors and peroxisome activated receptors. This led to the deposition of lipids in the hepatic cells which could be explained by probable upregulation of lipogenesis as these genes are associated with fatty acid biosynthesis. Such lipid deposition was seen to be independent of food/diet. The elevated lipids were mainly triglycerides, cholesterol, and phospholipids, all of which were elevated within 48 hours of clozapine dose [14-23].

Clozapine role in alteration of lipid

Ferno, et al. recognized a bunch of upregulated genes concerned with the biosynthesis of cholesterol and fatty acids, which were operated by SREBP transcription factors. This examination of the gene expression profile mainly the human glioma cells was manifested when exposed to both clozapine and haloperidol. This observation was done by use of a microarray technique. The upregulated genes caused lipogenesis in the cell which probably could explain the metabolic effects of antipsychotic drugs. An interesting fact about clozapine is that it has an increased therapeutic effect when

compared with other typical antipsychotic drugs (e.g., haloperidol, and chlorpromazine) in treating refractory schizophrenia. In his study, the concentration of haloperidol (10 μm) and Clozapine (30 μm) that showed SREBP activation in the glioma cultures comparatively were approximately 400 and 5 fold higher than the borderline therapeutically efficient levels of these drugs. The upregulation of the genes involved in lipid biosynthesis also occurred at 10 μm of clozapine, which again is fivefold above the therapeutically efficient level. It seems possible that clozapine may induce the activation of SREBP thereby causing lipogenesis *in vivo*. Many of the biochemical pathways which involve the SREBP system seem to be altered by numerous AAPD (Figure 2). Clozapine drug can bring about a notable upregulation of SREBP-1 and SREBP-2 and the downstream regulation of the same genes leading to enhanced lipid and cholesterol synthesis as noted with a single intraperitoneal injection of clozapine which induced a marked elevation of free fatty acids, followed by accumulation of lipids in the liver [24-32].

Figure 2. Mechanism of action, pros and cons of clozapine.



In the white adipose tissues, a biphasic pattern *i.e.*, initial upregulation followed by down regulation of SREBP controlled lipogenic genes correlating with rapidly decreasing drug concentration were seen. An upregulation of genes associated with pathways like biosynthesis of fatty acids (especially Fasn), adipogenesis (e.g.: Pparg), and cholesterol biosynthesis (HMG-CR gene *i.e.* 3-Hydroxy-3-Methylglutaryl-CoA Reductase) were displayed by mesenteric white adipose tissues. Similar effects were observed by Jassim, et al., in the ovarian WAT as well. One plausible mechanism in Jassim, et al., study was that the increase in serum free fatty acids is quick and is lipase mediated. The degradation of triglycerides also is instant in the White adipose tissue. This theory is propped up by the rapidly increased lipase gene expression (such as Hsl, Lpl), in both the ovarian as well as mesenteric WAT. The conversion of saturated fatty acids into monounsaturated fatty acids is catalyzed by the Stearoyl CoA Desaturase (SCD1) enzyme which is a rate-limiting enzyme, and this enzyme is also involved in the *de novo* synthesis of triglycerides, cholesterol esters, and phospholipids. This SCD1 is a target of the SREBP system and can directly influence lipid homeostasis. Numerous studies have shown that antipsychotic induced upregulation of SREBP-controlled lipogenic genes mainly includes SCD1. Rapid lipolytic activity in WAT, followed by elevation of free fatty acid in serum may give rise to a stressful situation like an increase in sympathetic nervous activity and release of catecholamines. Thus, establishing a relationship between clozapine and alpha 2-adrenoceptors, in this sense, clozapine does block the antilipolytic alpha 2 adrenoceptors [33-39].

Atypical antipsychotics, particularly clozapine can increase weight and bring about accumulation of lipids in the adipose

tissue by decreasing lipolysis *i.e.*, mainly the hydrolysis of triglyceride. In-fact, there is enough confirmed evidence in schizophrenic patients which indicates that antipsychotic drugs is associated with a high adiposity. It is the SREBP1 system that is demonstrated to be up regulated in the liver and the adipose tissues of the rats that were treated with atypical antipsychotics and exhibited dyslipidemia, suggesting that this mechanism may be involved in inducing dyslipidemia. Suppression of insulin release, insulin resistance, and impairment of glucose utilization by the cells could also explain the adverse metabolic outcomes caused by clozapine [40-45].

Clozapine and role of Phospholipids

A study by Correia, et al., who tested alterations in lipid content after clozapine drug treatment for 30 days showed potential changes in lipids that contributed to a better understanding of metabolic derangement while treating schizophrenics with any antipsychotic drugs under clinical conditions. The results showed elevation in cholesterol, saturated and unsaturated fatty acids *i.e.*, omega 3 and omega 6 fatty acids, cardiolipins, phosphocholine, and sphingomyelins. His results were agreeing with previously recorded down regulation of phosphocholine as done by Daouk, et al [46-49].

DISCUSSION

Clozapine modifies lipids to a higher degree in comparison to treatment with haloperidol. Antipsychotics bring about a marked decrease in chemical shifts in PUFA and omega 3 fatty acids. Alongside the decrease in PUFA (specifically omega 6) and phospholipid levels observed after clozapine treatment, choline and glycerophospholipids were also decreased by Clozapine. These important PUFAs like omega-3, omega-6, and phospholipids could be incorporated into glycerophospholipids, the role of which is important in the cell membrane. It was suggested that accumulation of cholesterol in the nigrostriatal pathway could contribute to dopaminergic degeneration of neurons in the mice brain. This observation came from a significant presence of cholesterol in the blood of schizophrenic animals during experimentation, also proposed to induce cognitive dysfunction in experimental animals. Moreover, excessive utilization of phospholipids from the brain membrane, insufficient biosynthesis of the same is also hypothesized to relate to schizophrenia and nonfunctional synapses. So, a greater level of phospholipids in clozapine treated animal models could indicate a possibility of de-novo synthesis of phospholipids to meet the deficiency [50].

CONCLUSION

In this review, an examination of dyslipidemia induced by clozapine drug treatment in schizophrenia disorder has been made. Generally, patients treated with clozapine have major concerns about weight gain and express a desire to be active and always lean. Although, antipsychotics such as clozapine carries marked metabolic burden; it remains to be a choice of drug for patients who usually do not respond to conventional antipsychotics. Most of the results confirmed that antipsychotic treatment provokes a significant increase in lipid parameters. Evidence shows that metabolic syndrome is highly prevalent among schizophrenic patients. Possibly several factors interact to increase this risk in schizophrenic patients. Hence, in the current scenario, repeated monitoring of serum lipids is needed to curb the metabolic syndrome. More research is needed to elaborate the mechanism as to how each factor operates to increase metabolic syndrome risk. Further, we need to examine whether the contributions of these factors differ geographically.

Monitoring of lipids and glucose during clozapine therapy is required to get a better understanding of Clozapine's

impact, thereby, permitting the invention of novel drugs without any limitation. Also, lipid lowering agents could be effective in reducing total serum cholesterol, LDL Cholesterol, and triglycerides. There is need to explore natural agents in plants which could be potential therapy in human ailments. Family can be the best caregivers to their loved ones and so it is important to equip the family with adequate knowledge about schizophrenia and home management. The review findings strongly support the hypotheses that patients on clozapine treatment do experience concerning weight gain and lipid derangement and hence, are likely to be at high risk of developing cardiovascular diseases. Further risk management strategies need to be added during Antipsychotic treatment like lifestyle interventions and lipid lowering agents, to try and control bad effects of such risk factors.

Competing Interests

"The authors have no relevant financial or non-financial interests to disclose."

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