Improving the treatment of schizophrenia psychology essay

Schizophrenia is a disorder that is characterised with some of loss of contact with reality and symptoms often consist of disruption of thought, perception, mood and movement. Schizophrenia can consist of positive or negative symptoms. Patients with positive symptoms often experience delusions, hallucinations, and often show disorganised speech. They also tend to be significantly disorganised or conversely some may show catatonic behaviours, in which they may remain motionless for a long time. However, negative symptoms reflect the absence of responses that are normally present, these include reduced expression of emotion, poverty of speech, difficulty in initiating goal-directed behaviour and memory impairment. However several studies have suggested that positive symptoms are often easier to cure than the negative symptoms, using biological approaches such as drug therapy or cognitive or behavioural approaches such as cognitive-behavioural therapy. Yet, Schizophrenia affects about 1% of the population (Andreasen, 2000).

In the past and currently still the most dominant idea was that the dopamine system significantly accounted for the schizophrenic symptoms present in patients, specifically by the activation of the dopamine receptors. Consequently, the biological approach to treating schizophrenic symptoms consists of drug therapy by giving patients typical antipsychotic drug such as clozapine or haloperidol that target to block dopamine receptors.

However drug therapy using typical antipsychotics is only seen as effective in treating the positive symptoms in schizophrenic patients, whilst having limited effect on the negative symptoms (Chaves et al., 2009). Moreover, typical antipsychotics cause undesirable side effects, such as tardive

dyskinesia, extrapyramidal symptoms which includes unusual body or facial movements, rigidity and restlessness, these occur as a result of blocking the D2 receptors (Remington, 2003; Horacek et al., 2006). However, atypical antipsychotic drugs given in clinically effective dosages do not bring about these clinical side effects (Leucht et al., 1999; Seeman, 2002) because they are thought not to act directly on the dopamine receptors in the striatum. Studies have confirmed that the atypical are much better on the negative and affective symptoms, cognitive dysfunction and aggression (Remington, 2003). Researchers suggest that the reason behind this is that atypical antipsychotics such as clozapine and amisulpride have lower affinities for the D2 receptor and only bind loosely to the receptor and are rapidly released (Horacek et al., 2006; Seeman, 2002), than typical antipsychotics such as chlorpromazine and haloperidol. Although it has been shown by studies these drugs do increase weight in patients, they are still considered better than typical antipsychotics.

Moreover, it is known that clinically effective dosages of antipsychotic drugs occupy between sixty to eighty percent of brain D2 receptors in patient. However, clozapine and quetiapine only occupy between zero and fifty percent of brain dopamine D2 receptors (Seeman, 2002). Studies now suggest that because the atypical antipsychotics occupy many different types of receptors, symptoms caused by schizophrenia is a lot more complex than an overactive dopamine system and that D2 receptors are not the major antipsychotic target in schizophrenia. However, it can also been argued that clozapine and quetiapine work better with fewer side effects because they rapidly dissociate from the dopamine D2 receptors than typical

antipsychotics. Recently it has been suggested that clozapine may exert a more direct interaction with NMDA receptors than other antipsychotic drugs (Chaves et al., 2009; Krystal et al., 1994). Moreover, researchers have shown that clozapine acts as partial agonists at the glycine modulating site of the NMDA receptor, at low concentration it increases neuronal depolarization and at high concentrations it inhibits depolarization which explains why clozapine works better than typical antipsychotics.

Current antipsychotic drugs affect glutamatergic activity in many ways, such as enhancing release of glutamate in the striatum, changing glutamate receptor density and directly interacting with NMDA receptors. Many of these effects vary between the antipsychotic drugs, with important differences seen between atypical and typical drugs. New clinical trials which have been conducted in which NMDA receptor activity was improved by drugs acting at the glycine modulatory site of NMDA receptor have shown a decrease in the negative symptoms and improvements in patients cognitive function (Goff and Coyle, 2001).

Most research evidence suggests that the effects of certain atypical antipsychotics on the NMDA receptors may tell between these drugs from typical antipsychotics are the reason they work better on schizophrenic patients in treating their symptoms. Researchers found that haloperidol which is a typical antipsychotic did not significantly interact with NMDA receptors at clinically relevant concentrations but that clozapine which is an atypical antipsychotic did displace the ligand from the NMDA receptor at therapeutic levels. This again provides more evidence that modulation at the

NMDA receptor may be a better therapeutic target. As research already agrees that clozapine works better than haloperidol.

Glutamatergic neurons are the major excitatory pathways linking the limbic system, cortex, and thalamus and these regions that have been implicated in schizophrenia. Therefore, researchers have proposed the idea that glutamate system is a worthy strategy to treat schizophrenia. So according to this, the schizophrenia is a result of diminished activation of NMDA receptors in the brain, than an overactive dopamine system. This hypothesis was supported by phencyclidine, ketamine, and other NMDA-R antagonists blocks the NMDA receptor so in healthy volunteers produces symptoms and cognitive impairments very close to schizophrenia (Krystal et al., 1994; Hashimoto et al., 2003), and it also increases dopamine release in the mesolimbic system (Goff and Coyle, 2001). The NMDA receptor antagonist induced psychosis models the cognitive deficits and the negative symptoms better than the dopamine model (Krystal et al., 1994; Hashimoto et al., 2003), so the action of NMDA receptors is a promising treatment for schizophrenia. In therapeutic trials, drugs that indirectly improve NMDA receptor function have been shown to reduce negative symptoms and improve cognitive functioning in schizophrenic patients. Moreover, in clinical trials in which drugs that enhance NMDA receptor activity have shown to improve symptoms in schizophrenic patients (Goff and Coyle, 2001). Experiments have been carried out on full and partial agonist such as glycine, D-serine and sarcosine (Kantrowitz and Javitt, 2010).

Moreover, in the case of haloperidol, synaptic plasticity has been particularly well documented in the striatum, where the highest concentration of D2

receptors exists (Horacek et al., 2006). However, some studies have shown that by blocking D2 receptors in the striatum does not reduce the symptoms of working memory impairments. Therefore, it has been suggested that direct modulation of hyperactive NMDA receptors by drugs like acamprosate may allow us to target microcircuits within the mesocortico, which are not accessible to conventional D2 based treatments to help treat schizophrenia (Paz et al., 2008).

In the experiments, acamprosate has been shown to act as an antagonist when the NMDA receptors are maximally stimulated but acts as an agonist when NMDA receptor stimulation is minimal. Researchers predict using research done that this drug would enhance the function of NMDA receptors in schizophrenia and improve cognition and the symptoms of the illness.

Tuominen et al., 2005, published review and meta-analysis, and found out that D-serine and glycine was a success in reducing the negative symptom. However, there was no major effect of D-serine or glycine on the positive symptoms cognitive functions. Therefore, Shim et al., 2008, said in their article that other drugs could be effective by acting on other sites of the NMDA receptors in the treatment of schizophrenia as research in glutamatergic drugs is still in its early years of research.

Another drug called minocycline that researchers have been tested to see its possible effects in treating symptoms of schizophrenia. Even though the exact mechanism of action of minocycline remains vague, the latest studies conducted with minocycline suggest that it does modulate the glutamatergic system. In animal studies minocycline reversed several NMDA-R antagonist

effects such as phencyclidine and ketamine and showed positive results in treating the symptoms of schizophrenia. This suggests that minocycline indirectly modulates NMDA-R transmission. Moreover recent work with an ampakine also indicated that positive modulation of the AMPA receptor may also provide another glutamatergic approach to treat cognitive deficits in schizophrenia (Goff and Coyle, 2001).

Although the findings are preliminary, it is now suggested that dysfunction of glutamatergic neurotransmission plays a significant part in treating the symptoms of schizophrenia, especially of the negative symptoms and cognitive impairments and it is a promising target for drug development (Goff and Coyle, 2001). Researchers that looked into developing drugs that restore the hyperglutamatergic state by normalizing the abnormal NMDA function without altering the balance of synaptic and extra synaptic glutamatergic transmission has been found to be useful for schizophrenic patients.

Due 4th march at 12PM at AC and pharmacology-admin@kcl. ac. uk