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BENZODIAZEPINES IN COMBINATION WITH ANTIPSYCHOTIC DRUGS FOR SCHIZOPHRENIA: GABA-ERGIC TARGETED THERAPY

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SUMMARY

Antipsychotics are a key intervention strategy in pharmacotherapy of schizophrenia. However, benzodiazepines are often prescribed to control sleep disturbances, anxiety or behavioural disinhibition. There is clinical evidence for the beneficial effect of the combined treatment of antipsychotics and benzodiazepines resulting in more favorable treatment outcome in schizophrenia with regard to positive and negative symptoms. This clinical phenomenon seems to be associated with the GABA-ergic activit ythat is believed to be disrupted in the schizophrenia and direct benzodiazepines effect on GABA-A receptors.

In the brain there are both excitatory and inhibitory neurotransmitters which cooperate between themselves maintaining the proper functioning of the brain. GABA neurons carry inhibitory signals that help keep brain activity at optimal levels of operation, Glutamate, on the other hand, carry excitatory signals. As the interplay between these two exists they keep the dopamine levels in the average levels. The disruption of GABA-ergic transmission in schizophrenia may induce alternations in dopaminergic neurotransmission providing no inhibitory effect to the central glutamate activity, resulting in the rise of the dopamine levels being associated with psychosis precipitation.

Benzodiazepines are believed to reduce presynaptic dopamine release at the mesolimbic level and delay postsynaptic adaptation of dopaminergic neurons to antipsychotics potentiating the action of antipsychotics in resistant schizophrenia. Benzodiazepines also act on mesocortical regions where antipsychotics are less effective and where there is a particular sensitivity to stress.

This association is particularly useful in resistant patients or in patients with severe anxiety with or without intolerance to antipsychotics. Improvement concerns anxious symptoms but also positive symptoms (hallucinations, delirium and dissociative syndrome) and negative (social withdrawal, affect flattening).

As the available studies are limited there is some clinical evidence that the use of antipsychotic drugs with addition of benzodiazepines can provide better general outcome in ill patients than antipsychotics administration alone.

Key words: *schizophrenia - pharmacotherapy - antipsychotics - benzodiazepines - anxiety - residual symptoms*

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INTRODUCTION

Schizophrenia is a severe and disabling mental disorder characterized by thinking disruptions, affecting the sense of self, language and one's perception. Basing on Crow's nosology of symptoms in schizophrenia two symptoms domains are seen: positive (hallucinations, delusions, thought disorder) and negative (poverty of speech, flattening of affect, social withdrawal). The complexity and variability of symptoms pose a major challenge to the therapeutic interventions. However, contemporary antipsychotic medication, although effective in the positive symptom domain, often hardly addresses negative symptoms of the disease. Therapeutic actions of conventional antipsychotics are due to D2 receptor blockage, especially in the mesolimbic pathway. Atypical antipsychotic drugs exert therapeutic action mechanism mostly by blocking 5HT2A receptor as well as D2 receptors. The partial dopamine agonists are the third type of antipsychotic drugs stabilizing dopamine transmission in the brain by balancing the outputs of presynaptic and postsynaptic D2 receptors. Although newer atypical antipsychotics can have less affinity for dopamine receptors and still reduce positive symptoms, they do not adequately address the reduction in negative symptoms of schizophrenia.

DOPAMINE AND GABA NEUROTRANSMISSION IN SCHIZOPHRENIA

There are at least five subtypes of dopamine receptors, D1, D2, D3, D4, and D5. The D1and D5 receptors are members of the D1-like family of dopamine receptors, whereas the D2, D3 and D4 receptors are members of the D2-like family. There is also some evidence that suggests the existence of possible D6 and D7 dopamine receptors, but such receptors have not been conclusively identified (Contreras 2002). Dopamine receptors play an important role in the reward system, incentive salience, cognition, prolactin release, emesis and motor function. There are four dopamine pathways in the brain. One linked to positive symptoms of psychosis is the mesolimbic dopamine pathway which projects from dopaminergic cell bodies in the ventral tegmental area of the brainstem to axon terminals in limbic areas of the brain (e.g. nucleus accumbens). Substances which increase dopamine secretion (e.g. cocaine) increase dopamine signaling inducing/enhancing positive symptoms of schizophrenia. On the other hand, substances which decrease dopamine levels, such as antipsychotic drugs, reduce the symptoms of psychosis. Do date all known antipsychotic drugs are dopamine receptors antagonists (mainly D2 type). The hyperactivity of the mesolimbic

pathway either primary or secondary is believed to be responsible for symptoms like auditory hallucinations, delusions, thought disorders.

Although dopaminergic overactivation in the mesolimbic system is the key mechanism for psychosis in schizophrenia GABAergic dysfunction is among other proposed mechanisms to be considered. As GABAergic transmission is vital in modulating cortical activity the altered receptor activity and pharmacology would disrupt normal neural processing, resulting in an imbalance in other systems, and symptoms of schizophrenia (Hinton 2008). As for GABA itself is the chief inhibitory neurotransmitter being abundant in the mammalian central nervous system.It plays the principal role in reducing neuronal excitability throughoutthe nervous system. In humans, GABA is also directly responsible for the regulation of muscle tone (Wantanabe 2002). The highest GABA levels in a human brain are located in the dopamine-rich basal ganglia. GABA-containing neurons there are intrinsic to the striatum, form a long feedback-loop path from the striatum to the substantia nigra pars reticulata and globus pallidus and constitute a major efferent pathway from the substantia nigra to the thalamus, superior colliculus and reticular system. These tracts modify dopaminergic function in these and other sites by decreasing presynaptic dopamine release. The inhibition of GABA input to dopamine neurons in the ventral tegmental area results in increased dopamine activity in the nucleus accumbens and olfactory tubercule. Reynold et al. reported a lower than normal density of GABA uptake sites in hippocampus samples from the autopsied brain of schizophrenic patients; this deficit was correlated in the left hemipshpere with higher than normal dopamine concentrations in the amygdala (Wolkowitz 1996). The GABA receptors may be divided in three groups: GABAA, GABAB, GABAc. The role of GABAA receptor protein complex as the molecular target of the benzodiazepines but there is a little knowledge on GABA in the schizophrenic process.

Glutamate (working through NMDA receptors) a main excitatory neurotransmitter in the brain, was linked to the other than dopamine model of schizophrenia. The glutamate hypothesis proposes the hypofunction of NMDA receptors preventing glutamate from binding to the receptor increasing excitotoxicity glutamate levels, which induce schizophrenia symptoms. The blockade of NMDA receptors in the anterior thalamus may be the key step leading to cortical glutamate release (Graham 2016).

Schizophrenia is also characterized by loss of brain volume which may represent an ongoing excitotoxic pathophysiological process. This loss of brain volume may be explained by reduced neuropil rather than neuronal loss suggesting abnormal synaptic plasticity and cortical microcircuitry. A possible mechanism is hypofunction of the NMDA-type of glutamate receptor, which reduces the excitation of inhibitory GABAergic interneurons, resulting in a disinhibition of glutamatergic pyramidal neurons. Disinhibition of pyramidal cells may result in excessive stimulation by glutamate which, in turn, may cause neuronal damage or death through excitotoxicity. The main finding is a significantly lower GABA/Cr ratio in the prefrontal cortex in patients with schizophrenia as compared to healthy controls. In addition, the lower prefrontal GABA/Cr ratios were associated with higher levels of general cognitive functioning in the patients. No significant difference in the GABA/Cr ratio was found between patients and controls in the parieto-occipital cortex (Marsman 2016). In schizophrenia there are activity changes in dopamine tracts which are responsible for positive and negative symptoms of the disease. The structural anomalies in GABA where found in post mortem brain examination of schizophrenic patients. Altered cortical GABA neurotransmission appears to contribute to disturbances in diverse functions through affecting the generation of cortical oscillations in schizophrenia. The disturbances in cortical GABA neurons may strongly contribute to symptoms like overinclusivness or thought disorganization. In the limbic system it can contribute on the other hand with pale or parathymic affect in schizophrenia, due to the limbic system role in emotion processing (Wysokiński 2016). It also can provide neurocognitive decline especially in operative memory (Hashimoto 2010).

Drugs that act as allosteric modulators of GABA receptors (known as GABA analogues or GABAergic drugs) or increase the available amount of GABA typically have relaxing, anti-anxiety, and anti-convulsive effects. Many of the substances are known to cause amnestic effect. The most prescribed medication that have that effect are benzodiazepines. The main use of benzodiazepines is to cause sedation or in catatonia treatment.

It may be hypothesized that this stimulation of GABA with benzodiazepines leads to a secondary decrease in dopaminergic transmission resulting in an improvement in positive symptoms. Benzodiazepines also act on mesocortical regions where antipsychotics are less effective and where there is a particular sensitivity to stress.

A 4-week double-blind study in schizophrenic patients showed that reduction in the volume of the prefrontal cortex, combined with an exaggerated stress dopaminergic response, was predictive of a better response to alprazolam. Wassef et al., in a review of the use of GABA-ergic drugs, also hypothesize efficacy on hypofrontality through the action of these substances on mesocortical areas. This association is particularly useful in treatment resistant patients or in patients with severe anxiety with or without intolerance to antipsychotic. Improvement concerns anxious symptoms but also positive symptoms (hallucinations, delirium

and dissociative syndrome) and negative (social withdrawal, affect flattening). Therapeutic benefit in the treatment of schizophrenia have been documented for at least 5 different BDZ: chlordiazepoxide, diazepam, alprazolam, lorazepam, estazolam (Parkar 2011). However, the majority of clinical researche swere performed in the 1960s, mostly uncontrolled, often on small materials of mixed composition and with less-than adequate definition of the various patient subgroups. In general the conclusions drawn from the different studies are often highly diverging, more than in most other fields of clinical psychopharmacology.

DISCUSSION

As GABA neurons carry inhibitory signals that help keep brain activity at optimal levels of operation, glutamate, on the other hand, carries excitatory signals. As the interplay between these two exists they are keeping the dopamine levels in the average levels. There is some evidence that GABA disruption in schizophrenia can lead to fluctuation of dopamine levels bypassing the glutamate actions inhibition mechanism, causing secondary rise in the dopamine levels that may induce psychosis. Benzodiazepine use and with their pharmacodynamic effect on GABA neurons may contribute to the restoration of the dopaminergic activity in balancing dopamine, GABA and glutamate transmission exerting a therapeutic effect on both positive and negative symptoms of schizophrenia (Figure 1). Augmentation of antipsychotics with benzodiazepines is associated with drug-induced dopamine decrease in the prefrontal cortex of the brain, which gives a synergistic effect with antipsychotic drug action in the mesolimbic-cortical-striatal mechanism.

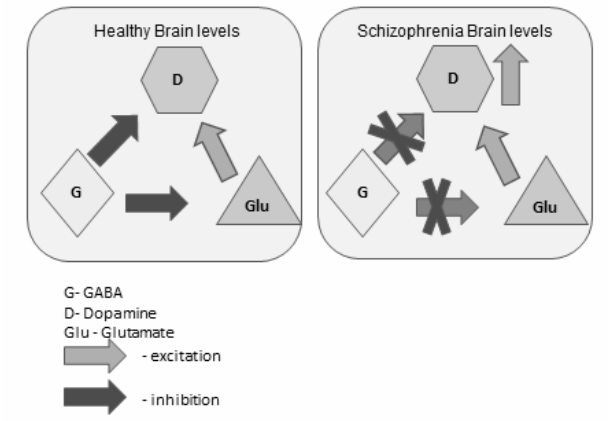

Figure 1. The interplay of Dopamine, Glutamate and GABA in the human brain

The specific benzodiazepine selection might be of importance, since they differ in both pharmacokinetics and pharmacodynamics. Although there are some studies which were negative on benzodiazepine- antipsychotic combination, there is some evidence for a beneficial effect of BDZs when given as add-on treatment to antipsychotics. The type of schizophrenia might be another variable as the majority of positive results in studies obtained were in chronic schizophrenic patients.

The studies on add-on treatment with benzodiazepines in schizophrenic patients receiving antipsychotics indicate the therapeutic effect on symptoms like anxiety, restlessness, tension but also on hallucinations, delusions, and other symptoms considered as more typical of psychoses. It may be indicative that benzodiazepines may potentiate the therapeutic efficacy antipsychotics (Gaillard 2006). The antipsychotic-benzodiazepine combination treatment may be a therapeutic option to be considered in schizophrenic patients with predominant negative symptomatology and challenging difficulties in the achievement of remission.

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