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Metabotropic glutamate receptors in the tripartite synapse as a target for new psychotropic drugs

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ABSTRACT

Mental disorders, such as depression, anxiety and schizophrenia, has become a large medical and social problem recently. Studies performed in animal tests and early clinical investigations brought a new insight in the pharmacotherapy of these disorders. Latest investigations are focused mainly on the glutamatergic system, a main excitatory amino acid neurotransmitter in the brain. Evidence indicates that metabotropic glutamate receptors ligands have excellent antidepressant, anxiolytic and antipsychotic effects. Metabotopic glutamate receptors (mGlu) divaded into three groups (group I, II and III) are localized on nerve terminals, postsynaptic sites and glial cells and thus they can influence and modulate the action of glutamate on different levels in the synapse. Recent advances in the identification of selective and specific compounds (both ortho- and allosteric ligands), and the generation of transgenic animals enabled to have new insight into the pathophysiology and therapy of mood disorders. At present, the most potent seem to be negative allosteric modulators of the first group (mGlu1 and mGlu5), and positive allosteric modulators of the second (mGlu2 and mGlu3) and third (mGlu4/7/8) group of mGlu receptors.

1. Introduction

Psychiatric disorders are a group of mental diseases with the highest rates of disability (Melzer et al., 2003). In Europe, over 70 million are affected by depression, anxiety, or schizophrenia, which, in most cases, prevent them from conducting a normal social and professional life. The problem becomes greater every year as more people are diagnosed with psychiatric disorders (Melzer et al., 2003). Moreover, the treatment is usually expensive, may last for a long time with little success, and a number of serious adverse effects occur in most cases. The lack of effective treatment is partially caused by the heterogeneous nature of disorders with multiple molecular, environmental and genetic factors, some of which are not fully understood. In this review, we tried to focus on some aspects of pathology and pharmacotherapy of mental disorders, paying special attention to the role of glial cells, in addition to summarizing the latest knowledge concerning the future perspective of treatment as well as speculating as to the probable mode of action of newly synthesized psychotropic agents.

2. Current treatments

In the European Union, anxiety disorders constitute the most prevalent psychiatric disturbance, affecting the greatest number of people, with more than 40 million people suffering from mental illness. The cost of treating anxiety disorders is very high, reaching approximately 42 billion dollars per year. However, although treating anxiety is expensive, the highest cost of treatment is for major depression, and it reaches up to 105 billion Euro in the EU (Andlin-Sobocki et al., 2005). This disease is characterized by a chronic low mood and anhedonia (loss of interest or pleasure) (DSM-IV). Patients suffering from depression are mostly women and the most common time of onset is between the ages of 30 and 40, with a later peak between 50 and 60 (Cassano and Fava, 2002).

Schizophrenia is a third serious disorder, although not so common as anxiety or depression, with less than 1% of population suffering from the disease. This disorder is primarily thought to affect cognition, but also usually contributes to chronic problems with behavior and emotion (Goldner et al., 2002). In addition to major depression and anxiety, around 40% people with schizophrenia have problems with substance abuse (Brown et al., 2000). Late adolescence and early adulthood are the peak years for onset of disease. These periods are critical in social and vocational development and their disruption leads to problems like long-term

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unemployment, poverty, and homelessness, decreasing the patients' quality of life (Amminger et al., 2006).

Despite many years of intensive studies, the lack of effective psychotropic drugs without serious adverse side effects, together with the increasing number of people suffering from mental illnesses, make this a large medical and social problem. Although hundreds of different medications are offered by the pharmaceutical industry all over the world, efficient and safe drugs for treating central nervous system (CNS) disorders are still not available. The necessity of chronic administration of antidepressants, together with their low efficacy (around 65%) and adverse side effects (changes in body weight, nausea, sexual dysfunction, diarrhea) makes them insufficient and unsatisfactory (Kirsch, 2008; Turner and Rosenthal, 2008). On the other hand typical anxiolytic drugs, such as benzodiazepines (BDZ), although quite effective, are not without serious adverse side effects. The most common adverse side effects are sedation, miorelaxation, dangerous interactions with alcohol, amnesia, and development of tolerance or dependence after chronic administration (Nemeroff, 2003a).

Neuroleptics are divided into typical (e.g., haloperidol) and atypical (e.g., clozapine, olanzapine) groups (Lieberman et al., 2005; Leucht et al., 2003). The typical antypsychotics are effective in reducing "positive" but not "negative" symptoms of psychosis, which are major problems in the life of a schizophrenia patient (Leucht et al., 2003). They also induce severe extrapyramidal side effects due to chronic blockade of D2 receptors in the striatum (Leucht et al., 2003). The newer atypical antipsychotic drugs are usually preferred for initial treatment; they are often better tolerated and associated with lower rates of extrapyramidal side effects and are also more effective in reducing the negative and cognitive symptoms of psychosis. However, they are more likely to induce weight gain and obesity-related diseases (olanzapines) (Lieberman et al., 2005) or agranulocytosis (clozapine) (Haas et al., 2007).

Taking into consideration the problems with current treatments, it is necessary to look for new psychotropic drugs with the better efficacy, a faster onset of action, and fewer serious adverse effects typical of presently used psychopharmacotherapy (see text below).

The focus of our research concerning work done in the last 10 years has been aimed at glutamate, a chief excitatory amino acid in the brain. In the properly functioning CNS, neuronal excitability is the result of excitatory and inhibitory signals received by a single neuron or group of neurons by the number of excitatory (E) vs. inhibitory (I) contacts (Li et al., 2006a,b). In the mammalian CNS excitatory glutamatergic neurotransmission is balanced with the action of γ-aminobutyric acid (GABA), which is the main inhibitory amino acid neurotransmitter in the brain. Thus, the level of excitation is under the control of inhibition exerted by GABAergic neurons. The appropriate E/I balance is maintained by the mechanisms like homeostatic regulation of synaptic efficacy or proper expression of specific molecules that control synapse maturation and strength (Turrigiano and Nelson, 2004). Recently, non-neuronal cells like astrocytes have been implicated in modulating the excitation of both glutamatergic and GABAergic neurons by sequestering and releasing glutamate (Schousboe, 2003).

An imbalance between excitation and inhibition is also seen in the brains of patients with mental diseases such as anxiety, depression, or schizophrenia. Thus, it is likely that treatment should be focused on restoring the altered E/I synaptic ratio and the glutamatergic system seems to be a natural target for new therapeutic tools (Fig. 1).

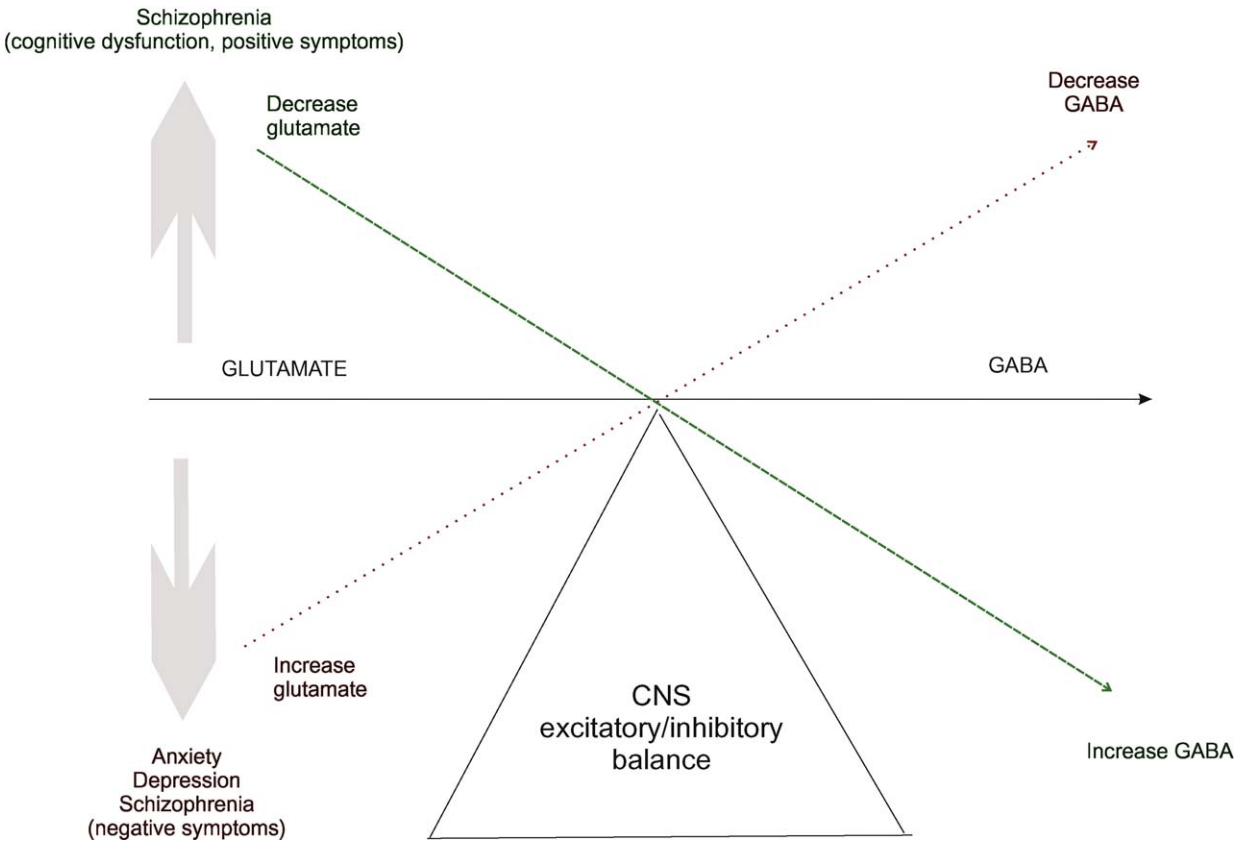

Fig. 1. A schematic representation of pathological imbalances in glutamatergic/GABAergic function in the CNS.