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Depression Viewed as a GABA/Glutamate Imbalance in the Central Nervous System

Joanna M. Wierońska[1], Agnieszka Pałucha-Poniewiera[1], Gabriel Nowak[1,2] and Andrzej Pilc[1,3]
[1]*Institute of Pharmacology, Polish Academy of Sciences, Kraków*
[2]*Jagiellonian University, Medical College, Department of Pharmacobiology, Kraków*
[3]*Jagiellonian University, Medical College, Faculty of Health Sciences, Kraków*
Poland

1. Introduction

Despite of the last few decades of investigations concerning the pathophysiology of affective disorders and their efficient treatment, the number of patients suffering from the diseases is growing every year. Compared to the data from the 1950s the percentage of people diagnosed with monopolar depression increased by nearly 7 times, and now it is estimated that more than 15% of the population suffers from the illness (Healy, 1999). Depressive episodes deeply influence the familiar and professional life of the patients, thus become both a clinical and social problem. The costs connected with the treatment are not only due to medical care, but also involve indirect wastes related to long-term disturbances in normal functioning. Statistical analysis reveal that depressive episodes became the most costly group of central nervous system (CNS) disorders in Europe and in the USA (in the recent decade they reached about 105 billion Euro and 83 Billion USD, respectively) (Andlin-Sobocki et al., 2005; Greenberg et al., 2003). Moreover, the problem of depression and mood disorders is hard to overestimate as only 1 out of 4 cases is either recognized or adequately treated, and approx. 15% of depressed people commit suicide (Brody et al., 1998).

The antidepressant pharmacotherapy presently used has been based on the modulation of monoaminergic neurotransmission (mainly noradrenergic and serotonergic). The accidentally discovered antidepressant activity of selective serotonin and noradrenalin reuptake inhibitors, as well as MAO inhibitors, laid at the grounds for the monoaminergic theory of depression (Kuhn, 1957; Loomer et al., 1957), which still dominates this field of research. The decreased level of monoamines in the depressed brain that was normalized after acute administration of antidepressant drugs (ADDs) became the main assumption of the hypothesis (Bunney et al., 1965; Lapin et al., 1969; Schildkraut, 1965). As the result of intensive studies, a number of antidepressant drugs were synthesized. However, most of them required chronic administration to evoke an antidepressant-like effect in humans. Therefore the increase in the serotonin and/or noradrenalin level in the brain observed immediately after the single administration of ADDs could not be responsible for the antidepressant effect observed only after several weeks of systemic treatment (for review

see: Castren, 2005; Oswald et al., 1972). Furthermore, in nearly 40% of patients the antidepressant therapy presently conducted is not effective, thus confirming the limited role of monoamines in depression.

The further research concerning antidepressant therapy was focused on the adaptive changes observed after prolonged antidepressant treatment. The progress of research lead to the discovery of the new receptors, second messengers systems, protein kinases, transcription and trophic factors, genetic and epigenetic regulations (Duman et al., 1997; Nestler, 1998; Nestler et al., 2002; Shirayama et al., 2002; for recent review, see Millan, 2006). A number of new hypotheses were proposed, and the neurotrophic theory of the disease was probably the mostly recognized. It was based on the observed increase in the BDNF level after prolonged ADDs treatment (Altar, 1999; Nibuya et al., 1995), which was supposed to be involved in the hippocampal processes of plasticity and neurogenesis (Altar, 1999; Duman et al., 1997; Duman et al., 1998; Nestler, 1998; Duman et al., 2001; Warner-Schmidt & Duman, 2006).

However, despite all of the research, there are no drugs that are active after a single administration in depressed patients. Therefore, the new insight into the mechanism of action of antidepressants, based on anything beyond monoaminergic neurotransmission, is highly desired. Excitatory glutamate and inhibitory GABA seem to be good candidates for our consideration.

2. Amino acids neurotransmitters and depression

It has to be realized that glutamate constitutes 50-60% of all neurotransmission in the brain and the remaining 40-50% is GABAergic (Storm-Mathiesen and Iversen, 1979; Winfield et al., 1980; Winfield et al., 1981). Therefore 90-99% of neurons (depending on the source) are GABAergic or glutamatergic, and less than 10% is left for all the others monoamines, neuropeptides and neuroendocrine neuromodulators. The fundamental aspect of the proper functioning of the CNS is keeping the excitatory/inhibitory physiological balance (Altamura et al., 1993; Linden and Schoepp, 2006; Yildiz-Yesiloglu et al., 2006). Any disruptions within this balance may lead to a brain dysfunction reflected as a mental disorder. Viewing the pathophysiology of depression through the GABA-Glu interaction may bring new solutions concerning its effective treatment. Schematic representation of the twisted GABA/Glu balance in affective disorders is shown on the Figure 1.

The results of the preclinical and clinical investigations confirm that disrupted activity within these two amino acid neurotransmitters may lay at the grounds of depression. The other data shows that standard ADDs influence the inhibitory and excitatory neurotransmission, which contributes to their efficacy. Generally it can be concluded that antidepressant drug diminish glutamatergic neurotransmission (Tokarski et al. 2008) and increase GABAergic neurotransmission. Using these results as our basis it could be suggested that the direct pharmacological manipulation on GABA or Glu neurotransmission may become a faster and more efficient way to treat depression (Kendell et al., 2005).

A number of important review papers concerning the role of GABA and/or glutamate have been published lately, such as Cryan & Slatery, 2010; Drago et al., 2011; Froestl, 2010; Ghose et al., 2011; Hashimoto, 2011; Mitchell & Baker, 2010; Sanacora et al., 2011. In this review we decided to focus on issues which were not covered in the above mentioned reviews, mainly on interactions between GABAergic and glutamatergic systems with the involvement of

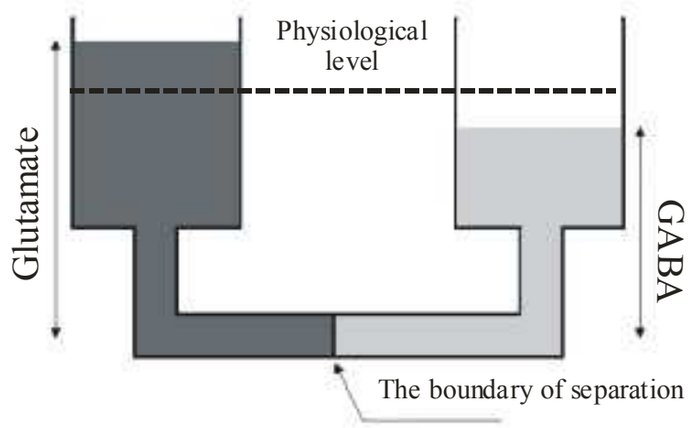


Fig. 1. The schematic representation of the Glutamate/GABA disbalance in the brain as an example of the communicating tubes. In the physiological conditions both liquids constitute a self-regulating system establishing the activity of both neurotransmitters on the same level. The disruption within the system leads to twist in the harmony, and the loss of the self-regulating properties. The overactivation of the glutamate and the decreased activity of GABA being responsible for mood disorders.

metabotropic receptors. This review is complementary to our recently published paper on the role of GABA and Glu interaction in anxiety (see Wieronska et at., 2011).

3. The role of the glutamatergic system in the treatment of depression

3.1 The role of the NMDA receptor in the mechanism of action of antidepressant drugs

The discovery and characterization of glutamatergic receptors opened a new possibilities to investigate the role of the glutamatergic system in the treatment of depression. The influence of the ADDs on the activity of glutamatergic receptors was studied on the one hand, whilst on the other hand the potential antidepressant effects of the ligands of those receptors were also investigated. Selected data are collected in Table 1.

The first reports on this subject concerned the NMDA receptor which belongs to the family of ionotropic receptor for the glutamate (together with AMPA and KA receptors). The receptor was described in details elsewhere (see: Danysz et al., 1998; Wieronska et al., 2011). The studies conducted in the 1990s revealed the antidepressant activity of the functional antagonists of the NMDA receptor, such as AP-7, MK-801, or ACPC in the forced swim test or tail suspension test (Trullas & Skolnick, 1990). The later studies carried out using those experimental procedures confirmed antidepressant activity of the other NMDA antagonists, such as CGP37849, CGP39551, memantine, eliprodil and zinc (Kroczka et al., 2001; Layer et al., 1995; Maj et al., 1992a; 1992b; Moryl et al., 1993; Przegalinski et al., 1997).

Despite of the evident antidepressant-like activity of NMDA receptor antagonists in simple screening tests, it was also shown that the compounds were active in commonly known models of depression. And thus MK-801, CGP37849, CGP40116 and ACPC (Papp & Moryl,

Author	Compound/dose	Species	Test
Maj et al., 1992a	MK-801 (0.3 mg/kg)	rats	Porsolt test
Maj et al., 1992b	CGP37849 (0.625-5 mg/kg) CGP39551	rats	Porsolt test
Moryl et al., 1993	Amantadine Memantine bifemelane	rats	Porsolt test
Papp &Moryl, 1994	MK-801 (0.3 mg/kg) CGP37849 (5 mg/kg) CGP40116 (5 mg/kg)	rats	Chronic mild stress
Papp&Moryl, 1995	ACPC (200)	rats	Chronic mild stress
Layer et al., 1995	Eliprodil (20-40 mg/kg)	mice	Porsolt test
Trullas &Skolnick, 1990	AP-7 ACPC MK-801	mice	Porsolt test Tail suspension test
Przegaliński et al., 1997	ACPC (200-400 mg/kg) CGP37849 (0.625-5 mg/kg)	rats	Porsolt test
Muhonen et al., 2008	Memantine (20mg/day)	human	Clinical study
Berman et al., 2000	Ketamine (0.5 mg/kg)	human	Clinical study
Zarate et al., 2004, 2005	Riluzol (100-200mg/day)	human	Clinical study
Zarate et al., 2006	Ketamine (0.5 mg/kg)	human	Clinical study
Nowak et al., 2003	Zinc (25mg/day)	human	Clinical study
Eby&Eby, 2006	Magnesium aspartate (125-300 mg/day)	human	Clinical study
Chouinard et al., 1990	Magnesium aspartate (40mg/day)	human	Clinical study
Siwek et al., 2009	Zinc (25mg/day)	human	Clinical study
Li et al., 2010	Ro 25-6981 (10 mg/kg)	rats	Chronic unpredictable stress
Preskorn et al., 2008	CP-101, 606	human	Clinical study

Table 1. Collected data concerning the antidepressant-like activity of the NMDA receptor antagonists (see also description in the text).

1994; Papp & Moryl, 1996) were active in chronic mild stress. Additionally, memantine and MK-801 were active in chronic unpredictable stress (Ossowska et al., 1997). Also, the antidepressant-like activity of MK-801 was evident in the olfactory bulbectomy model of depression (Redmond et al., 1997). Ro 25-6981, the subunit selective NR_{2B} antagonist, was found to exhibit rapid (24h) antidepressant-like effect in the FST (Maeng, 2008; Li et al., 2010).

The role of the NMDA receptor in the mechanism of action of ADDs was confirmed in the variety of biochemical (Nowak et al., 1993, 1996, 1998), electrophysiological (Bobula et al., 2003) and behavioural studies (Popik et al., 2000) in both rats and mice. All the results indicated a reduction of the NMDA receptor function after repeated administration of a variety of ADDs, as well as after electroconvulsive therapy. Receptor binding studies with the use of selective NMDA receptor binding sites radioligands revealed the decrease of glycine's affinity to its binding site (GLY_B) and to the abolishment of its ability to modulate glutamate binding sites in the NMDA receptor complex. The changes in mRNA synthesis and proteins of selected subunits of the NMDA receptor, and the changes in their mutual composition, were shown as being connected with the influence of the chronic ADDs administration on the NMDA receptor (Skolnick, 1999).

3.2 Glutamatergic theory of depression

The above noted results of the studies on the NMDA receptor have become the fundamental element of the glutamatergic theory of depression (Skolnick, 1999, 2009). The hypothesis was based on the results obtained in the studies on the role of trophic factors in depression (Duman, 1998; Skolnick, 1999). The brain-derived neurotrophic factor (BDNF) may decrease mRNAs for NR_{2A} and NR_{2C} NMDA receptor subunits, resulting in changes in their mutual composition and impartment in the NMDA receptor function in the matter resembling the effect of NMDA receptor antagonists (Brandoli et al., 1998). Therefore, the glutamatergic theory of depression states that the activation of BDNF, after ADDs administration, may lead to impartment of NMDA receptor function, which is commonly observed after administration of standard ADDs and NMDA receptor antagonists (Skolnick, 1999).

3.3 Antidepressant effects of NMDA receptor antagonists-clinical studies

The characteristic for ADDs behavioural effects obtained after administration of NMDA receptor antagonists in animal studies were confirmed in recent clinical trials. The antidepressant effect of memantine, a low-affinity, uncompetitive open channel NMDA receptor blocker, was observed in treatment-resistant patients with severe depression and comorbid alcohol dependence (Muhonen et al., 2008). However, another clinical study showed no antidepressant effect of memantine in patients suffering from major depression (Zarate et al., 2006). Thus, the clinical utility of memantine seems to be controversial.

Much more promising results were obtained with another NMDA channel blocker, ketamine. During initial studies, the drug was administered to patients with severe, long term, treatment-resistant depression, two weeks after cessation of standard pharmacotherapy (Berman et al., 2000; Zarate et al., 2006). Ketamine at a dose of 0.5 mg/kg was administered through intravenous infusion and the 21-degree Hamilton scale was taken to estimate the mental health of the patients. A statistically significant effect of ketamine was evident 24 hours after injection. The effect was similar or even greater than the effect of standard antidepressants such as venlafaxine, buprion or fluoxetine administered for the time period of 8 weeks. The effect of ketamine was observed until seven days after a single administration (Zarate et al., 2006). Another clinical study showed, that a single infusion of ketamine induced a rapid resolution of suicidal ideation in treatment-resistant patients suffering from major depression (DiazGrananos et al., 2010). Moreover, a rapid antidepressant effect was observed after a single dose of ketamine in depressive patients

with a family history of alcohol dependence (Phelps et al., 2009) and in electroconvulsive therapy-resistant patients (Ibrahim et al., 2011).

Another group of potential antidepressants are the divalent ions of zinc and magnesium, which are known to be NMDA receptor antagonists. The preliminary study by Nowak et al. (2003) showed the beneficial effects of zinc supplementation on standard antidepressant therapy with tricyclics and SSRIs in patients with unipolar depression. Then, a double blind, placebo- controlled study by Siwek et al. (2009) demonstrated that zinc supplementation enhanced the efficacy of imipramine and facilitated the treatment outcome in treatment-resistant depression. Several clinical studies indicated beneficial effects of magnesium supplementation in depression and depression-related or comorbid disorders, such as: major depression (Eby & Eby, 2006), mania (Pavlinac et al., 1979), bipolar disorder (Chouinard et al., 1990), and depression in elderly diabetic patients suffering from hypomagnesemia (Barragan-Rodriguez et al., 2008).

Clinical studies also showed the potential antidepressant activity of subtype-selective NMDA receptor modulators, which are supposed to be better and safer drugs than non-selective antagonists. Firstly, promising preclinical results showed the potential antidepressant-like effect of a selective antagonist of the NR_{2B} subunit, Ro 256981 (Maeng et al., 2008). Then, the clinical study of Preskorn et al. (Preskorn et al., 2008) confirmed the antidepressant effect of NR_{2B} subunit-specific NMDA receptor antagonist, CP-101,606 in a placebo controlled, double-blind study in patients with a treatment-refractory major depressive disorder.

This data strongly supports the hypothesis that glutamate receptors ligands may become more efficient antidepressants than the presently used pharmacotherapy.

The effectiveness of NMDA receptor antagonists is consistent with the notion of increased glutamatergic transmission in depression. However, the problem of profound adverse effects connected with the use of ketamine or the other NMDA receptor antagonists still remains unsolved; therefore the introduction of those compounds to the clinic requires further extensive preclinical and clinical studies.

3.4 Antidepressant effects of AMPA receptor ligands

The other member of the ionotropic glutamate receptors family, AMPA, was shown as being engaged in the mechanisms of antidepressant effects, too. A variety of animal studies indicate the potential antidepressant activity of the positive allosteric modulators (potentiators) of that receptor. Such effects were shown for LY392098, which was active in the forced swim test in mice and rats and in the tail suspension test in mice (Li et al., 2001, 2003). Furthermore, the compound induced an elevation of both the mRNA and BDNF protein level (Legutko et al., 2001), which stays in line with the trophic theory of disease. Another positive allosteric modulator of the AMPA receptor with antidepressant-like efficacy was LY451646. The potential antidepressant activity was shown in the forced swim test and in the tail suspension test (Bai et al., 2001). Moreover, LY451646 administration lead to the increase of neuronal proliferation in the hippocampus of the rat brain (Bai et al., 2003), and an increase of the level of BDNF mRNA and trkB, and to the enhancement of the BDNF protein synthesis (Maćkowiak et al., 2002). The potential antidepressant activity for AMPA potentiators in the preclinical studies was shown also for other compounds, such as CX546,

CX614, and LY404817 (Bai et al., 2001; Lauterborn et al., 2000). Additionally, the fundamental role of the AMPA receptor was also shown for ketamine activity, while the action of ketamine in the forced swim test and learned helplessness test was attenuated by AMPA antagonist, NBQX, indicating that AMPA activation is necessary for ketamine action in models of depression (Koike et al. 2011; Maeng et al. 2008).

3.5 The role of mGlu receptors in the mechanism of action of antidepressant drugs

The introduction of currently available NMDA receptor antagonists into the clinic is impossible because of the variety of profound adverse effects that can be triggered after their administration. Metabotropic glutamate receptors are a natural alternative target to influence the glutamatergic system. These receptors are responsible for the modulation, but not for the fast neuronal transmission (Nakanishi et al., 1992). The discovery of selective ligands of these receptors created a new possibilities in the therapy of variety of central nervous system disturbances, including psychiatric disorders.

Until now 8 subtypes of metabotropic glutamate receptors have been cloned. They were named from 1-8, according to the sequence homology, pharmacology and the second messenger system they activate. There can be several splice variants of selected subtypes of the receptors created by alternative splicing (Pin and Duvoisin, 1995; Pin et al., 1999), which makes them an established family of 21 subtypes known. At present mGlu receptors are divided into three different groups according to the sequence homology, pharmacology and the second messenger system they activate. And as such group I consists of $mGlu_1$ and $mGlu_5$ receptor subtypes, $mGlu_{2/3}$ receptors create the group II of mGlu receptors and the third group involve $mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$ receptors (Pin and Duvoisin, 1995; Pin et al., 1999; see: Wieronska et al., 2011).

3.5.1 The role of group I mGlu receptors in the mechanism of action of antidepressant drugs

Among all mGlu receptors, the greatest preclinical potential for possible antidepressant efficacy was shown for the ligands of the I group of mGlu receptors, especially the $mGlu_5$ subtype, which is localized in the brain structures known to be connected with emotional and motivational processes, such as the cortex, hippocampus and the amygdala (Romano et al., 1995; for review see Wieronska et al., 2010). The involvement of the NMDA receptor in the action of both compounds plays a substantial role, as a lot of evidence indicates that $mGlu_5$ receptors are physically and functionally linked with the NMDA receptor complex. The Homer family of proteins functions as a bridge between group I mGlu receptors and IP_3 receptors, as well as with Shank proteins, which are a part of the NMDA receptor-associated PSD-95 complex (Brakeman et al., 1997; Lujan et al., 1996; Tu et al., 1999; Xiao et al., 1998). The activation of the $mGlu_5$ receptor has been shown to potentiate NMDA receptor activity in the mechanism that requires G-protein activation (Attuci et al., 2001; Awad et al., 2000; Pisani et al., 2001), and antagonists of $mGlu_5$ receptors have been reported to decrease NMDA receptor activation (Doherty et al., 2000). Therefore, the inhibition of $mGlu_5$ receptors and antagonism towards the NMDA receptor evokes a similar effect in the brain. However, due to the indirect influence on the ion channel, side-effects typical for the channel blockers are not observed after MTEP or MPEP administration. The pathological changes within the receptor itself, and the malfunction of the $mGlu_5$/NMDA complex, may contribute to altered transmission in the CNS

of depressed subjects. The observed decrease of the $mGlu_5$ receptor in the PFC of patients with depressive symptomatology (Deschwanden et al., 2011) supports this speculation, indicating on the impartment in the function of the receptor. The concomitant decrease of the PSD-95 enchoring protein (Feyissa et al., 2009) indicates on the dysfunction of the NMDA receptor, too. Although there is no experimental data on this subject, a hypothesis can be raised that $mGlu_5$/NMDA receptors lose their colocalization in depressive illness and that MPEP/MTEP administration restores the functionality of the complex.

It was shown that the blockade of $mGlu_5$ receptors may exert the effect similar to NMDA receptor antagonists e.g attenuation of the NMDA receptor function (Doherty et al., 2000). Therefore, to begin with, attempts to investigate the potential antidepressant-like effect of the antagonists of $mGlu_5$ receptors were undertaken. As shown in Table 2 the selective orthosteric antagonist for this receptor, MPEP (Gasparini et al., 1999) and its derivative MTEP (Cosford et al., 2003), were active in the forced swim test in both rats and mice, and in the tail suspension test in mice (Belozertseva et al., 2007; Li et al., 2006; Palucha et al., 2005; Pilc et al., 2002; Tatarczyńska et al., 2001). Moreover, in the olfactory bulbectomy model of depression it was shown that chronic administration of those substances evoked behavioural effects similar to those observed after the administration of ADDs administration (Palucha et al., 2005; Pilc et al., 2002; Wieronska et al., 2005). On the other hand repeated MPEP administration lead to an increase in the expression of BDNF mRNA

Author	Compound/dose	Species	Test
Tatarczyńska et al., 2001	MPEP (1-20mg/kg)	mice	Tail suspension
Pilc et al., 2002; Wierońska et al., 2002	MPEP (10 mg/kg)	rats	Olfactory bulbectomy model of depression
Belozertsewa et al., 2007	MTEP (5 and 10 mg/kg) MTEP (25mg/kg)	rats	Porsolt test
	MPEP (10 mg/kg)	mice	Tail suspension test
	EMQMCM (1.25-10 mg/kg)	mice rats	Tail suspension test Porsolt test
	EMQMCM (5 mg/kg)	mice	Tail suspension test
Pałucha et al., 2005	MTEP (0.3-30 mg/kg) MTEP (1 mg/kg)	mice rats	Tail suspension test Olfactory bulbectomy
Molina-Hernandez et al., 2008	MTEP (5 and 10 mg/kg) EMQMC (1.5 and 2 mg/kg)	rats rats	Porsolt test Porsolt test
Li et al., 2006	MPEP (10-30 mg/kg) MTEP (3-30 mg/kg)	mice mice	Porsolt test Porsolt test

Table 2. Collected data concerning the antidepressant-like activity of the group I mGlu receptors ligands. MPEP, MTEP-mGlu5 antagonists; EMQMC-mGlu1 antagonist.

in the hippocampus of the rat brain, which remains in line with the neurotrophic theory of depression (Legutko et al., 2006). Additional evidence suggesting the important role of the NMDA receptor in the underlying antidepressant mechanism of the $mGlu_5$ receptor antagonist comes from the studies of Pomierny-Chamioło et al. showing, that the anti-immobility action of MTEP in the Porsolt test was inhibited by NMDA administration (Pomierny-Chamioło et al., 2010).

The antidepressant effects could be evoked not only after administration of $mGlu_5$ receptor antagonists, but also after blockade of $mGlu_1$ receptor subtype, the second representative of group I mGlu receptors, as its antagonist EMQMCM was effective in the tail suspension and forced swim test in mice (Belozertseva et al., 2007). The role of the first group of mGlu receptors in depression and in the mechanism of action of ADDs is confirmed by experiments illustrating the changes in both the reactivity and expression of the $mGlu_1$ and $mGlu_5$ receptors after chronic ADDs treatment in both rats and mice (Pilc et al., 1998; Smiałowska et al., 2002; Zahorodna et al., 1999).

Unfortunatelly there is a limited amount of clinical data concerning antidepressant action of $mGlu_5$ receptor antagonists. Fenobam, discovered in 1978 as a nonbenzodiazepine anxiolytic (Itil et al., 1978), was in 2005 described as an $mGlu_5$ receptor antagonist with indication on anxiolytic activity (Porter et al., 2005). The antidepressant effects of fenobam were also reported (Lapierre & Oyewumi, 1982). The recent study of Berry-Kravis et al. show the positive results of fenobam administration in the treatment of fragile X syndrome, without any significant adverse reactions (Berry-Kravis et al., 2011), opening the possibility to evaluate the antidepressant potential of that agent or other new substances, such as ADX10059, which is effective in gastro-esophageal reflux disease (Zerbib et al.,2011) or in the treatment of migraine (Marin & Goadsby, 2010), with no major adverse effects.

The $mGlu_5$/NMDA receptor complexes were shown to be localized predominantly postsynaptically (Lujan et al. 1996) and in the hippocampus and prefrontal cortex known to be involved in depression those receptors are extensively expressed on GABAergic interneurons (van Hooft et al., 2000; Zhou et al., 1997). Similarly to the proposed earlier mechanism of anxiolytic-like action of MPEP or MTEP (Wieronska et al. 2011), the $mGlu_5$ antagonists would initiate a repertoire of changes between interneurons and pyramidal neurons to induce feedback inhibition of increased excitation in the brain.

As shown on Fig. 2 the inhibition of GABAergic neurotransmission by $mGlu_5$ receptor antagonists may occur at multiple sites: the inhibition of postsynaptic neurotransmission [Fig. 2 (1)] and the presynaptic inhibition of GABA release (Chu et al., 1998) [Fig.2 (2)] lead to the disinhibition of intermediate interneuron, which in turn inhibits the glutamatergic target neuronal element. The presynaptic localization of the $mGlu_5$ receptor in the medial prefrontal cortex (mPFC) was described in rare cases (Romano et al., 1995), and the activation of those receptors facilitates the release of glutamate (Thomas et al., 2000). Therefore the blockade of mGlu5-mediated presynaptic neurotransmission could have an inhibitory effect on glutamatergic neurotransmission [Fig. 2 (3)]. The studies of Marek & Zhang from 2008 stay in line with such a hypothesis, by showing the inhibition of DHPG-induced spontaneous EPSCs by MPEP (Marek & Zhang, 2008). As such, it can be supposed that the compound inhibits the activity of glutamate through pre- and postsynaptic binding sites at the interneurons and pyramidal neurons.

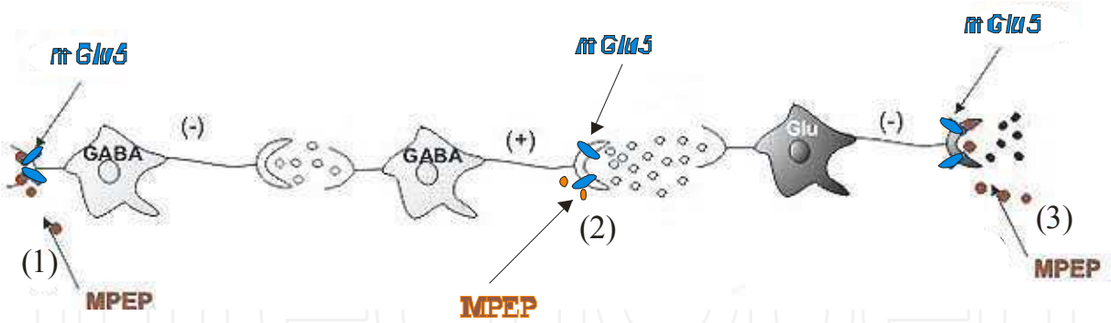


Fig. 2. The schematic representation of the mechanism of antidepressant-like action mediated by mGlu5 receptor antagonist(s) (see description in the text). Empty dots- GABA; black dots-Glu; (-)-inhibition; (+)-enhancement; the number of dots indicates the amount of neurotransmitter released

3.5.2 The role of group II mGlu receptors in the mechanism of action of antidepressant drugs

The investigations concerning the role of the II group of mGlu receptors was started with the orthosteric agonist of mGlu2/3 receptors, LY354740 (Helton et al., 1998). The compound was shown to be an effective anxiolytic, but not an antidepressant agent after peripheral administration in animal studies (Klodzinska et al., 1999). However, data on the antidepressant action of a novel $mGlu_2$ receptor potentiator THIIC (Fell et al., 2011) was recently reported, creating a hope for the antidepressant-like action for subtype selective agonists/PAMs.

As shown in Table 3 a number of experiments described the antidepressant-like activity of ligands of the $mGlu_{2/3}$ receptors. The best known selective and brain penetrating ligands of $mGlu_{2/3}$ receptors is MGS0039 (Nakazato et al., 2004). Another antagonist LY341495, is able to bind the third group of mGlu receptors too (Chung et al., 1997). Both compounds decreased the immobility time of animals in the Porsolt swim test or in the tail suspension test (Bespalov et al., 2008; Chaki et al., 2004). MGS0039 was shown to be active in the olfactory bulbectomy model of depression as well (Palucha-Poniewiera et al., 2010b). Moreover, the compound induced an increase in the neuronal proliferation in the rat hippocampus (Yoshimizu et al., 2004). The involvement of other than $mGlu_{2/3}$ receptor subtypes in the action of LY341495 cannot be ruled out, either as the compound is a mixed antagonist of both group II and group III receptors. The mechanism of the antidepressant-like action of both compounds was shown to be independent on the serotonergic system; the drugs were still active after the depletion of serotonin, and their action was not antagonized by serotonergic receptor antagonists ritanserin or WAY100635 (Pałucha-Poniewiera et al., 2010b). However, the activity of the compounds was antagonized by NBQX, further supporting the role of the AMPA receptor in the antidepressant action of $mGlu_{2/3}$ receptor ligands (Chaki et al., 2004; Karasawa et al., 2006; Kawashima et al., 2005; Palucha-Poniewiera et al., 2010b).

The possibility of involvement of the $mGlu_{2/3}$ receptor in depression was confirmed recently in the study of Feyissa et al showing the elevated level of the receptor in the prefrontal cortex of depressed suicide victims (Feyissa et al., 2010). These results correspond with the

Author	Compound/dose	Species	Test
Bespalov et al., 2008	LY341495 (0.3-3mg/kg)	mice	Porsolt test
Chaki et al., 2004	MGS0039 (0.3-3 mg/kg)	rats	Porsolt test
	LY341495 (0.1-3 mg/kg)	rats	Porsolt test
Karasawa et al., 2005	MGS0039 (0.3-3 mg/kg)	mice	Tail suspension test
Yasuhara et al., 2006	7ao (MGS0039 prodrug, 3-10 mg/kg)	rats	Porsolt test
		mice	Tail suspension test
Yoshimizu et al., 2006	MGS0039 (10mg/kg)	rats	Learned helplessness
Pałucha-Poniewiera et al., 2010b	MGS0039 (1-3 mg/kg)	rats	Olfactory bulbectomy
Fell et al., 2011	THIIC (10 mg/kg)	mice	Porsolt test

Table 3. Collected data concerning the antidepressant-like activity of the group II mGlu receptors ligands. MGS0039-mGlu2/3 antagonist; LY341495-mixed group II/III antagonist; THIIC-mGlu2 PAM.

reports showing the antidepressant-like activity of the antagonists of the second group of mGlu receptors.

The localization of $mGlu_{2/3}$ receptors in the synaptic junction is both pre- and postsynaptic, and it seems that neither of them is predominant (Petralia et al., 1996). As presynaptic auto- or heteroreceptors, $mGlu_{2/3}$ receptors are located at perisynaptic sites of the synapse, often along axon terminals. Such a localization enables on one hand for the pharmacological regulation of the neurotransmitter release and, on the other hand, to make the regulation of the postsynaptic neuronal element. The $mGlu_{2/3}$ receptors are inhibitory in nature, being negatively coupled to adenylyl cyclase activity, therefore their blockade on postsynaptic membranes of glutamatergic pyramidal neurons may lead to an enhancement of glutamatergic transmission [Fig.3 (1)]. A similar effect would be observed after the inhibition of presynaptic autoreceptors, leading to an overflow of glutamate [Fig.3 (2)] and the activation of an inhibitory GABA-ergic neuron, which then inhibits the glutamatergic output element. Alternatively the blockade of the $mGlu_{2/3}$ heteroreceptors by the ligands cannot be excluded in their overall action in the brain. The antagonism towards $mGlu_{2/3}$ heteroreceptors localized on GABAergic nerve terminals would activate the release of inhibitory neurotransmission and thus contributing to the abolishment of the overexcitation and to the antidepressant-like effect of MGS0039, in a way similar to standard antidepressants, which were shown to elevate the level of inhibitory amino acid in the CNS [Fig. 3 (3)].

The involvement of the glial element also seems to be important, either, as $mGlu_3$ receptors are widely distributed on those non neuronal cells (Petralia et al., 1996). This part of action of the $mGlu_{2/3}$ antagonist may be especially important in the depression, as astrocytes were shown to contribute to the pathophysiology of the illness (for review see: Wierońska & Pilc, 2009).

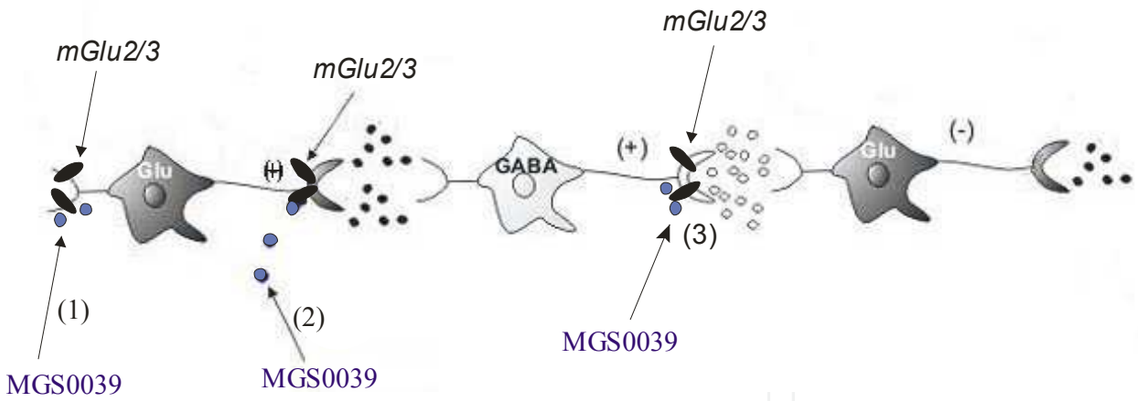


Fig. 3. The schematic representation of the mechanism of antidepressant-like action mediated by mGlu2/3 receptor antagonist(s) (see description in the text). Empty dots-GABA; black dots-Glu; (-)-inhibition; (+)-enhancement; the number of dots indicates the amount of neurotransmitter released

3.5.3 The role of group III mGlu receptors in the mechanism of action of antidepressant drugs

The third group of mGlu receptors is the largest and the least investigated. The lack of the selective and brain penetrating agents limited the investigations. Some results were obtained after the central administration of selected ligands such as ACPT-I and RS-PPG, which were shown to evoke a dose-dependent decrease in the immobility time after intrahippocampal administration (Palucha et al., 2004). However, the recent data obtained after peripheral administration of ACPT-I or LSP1-2111 did not indicate on any antidepressant-like efficacy (Stachowicz et al., 2009; Wieronska et al., 2010) of those preferential $mGlu_{4/8}$ receptor agonists (Acher et al., 1997; Beurrier et al., 2009). The $mGlu_7$ receptor was studied more extensively with the use of its positive modulator, AMN082. It was shown that the drug possessed antidepressant-like activity in the forced swim test in rats and mice, and in the tail suspension test in mice (Palucha et al., 2007, Table 4). Furthermore, the mechanism of the antidepressant action of the compound was shown to be serotonin-dependent, as it was absent in pCPA-treated animals and was inhibited by WAY100635, $5\text{-}HT_{1A}$ antagonist (Palucha-Poniewiera et al., 2010a). The involvement of $mGlu_7$ receptors in depression and in the mechanism of action of ADDs was confirmed by experiments showing the changes in the expression of the $mGlu_7$ receptor after standard antidepressant drugs, and in the olfactory bulbectomy model of depression (Wieronska et al., 2007, 2008).

Author	Compound/dose	Species	Test
Pałucha et al., 2007	AMN082 (3-6 mg/kg)	mice	Tail suspension test Porsolt test
Pałucha-Poniewiera et al., 2010	AMN082 (5-10 mg/kg)	rats	Porsolt test

Table 4. Collected data concerning the antidepressant-like activity of the group III mGlu receptors ligands. AMN082-mGlu7 positive modulator.

The receptor is expressed in the center of the synapse that is directly involved in the regulation of the neurotransmitter release, even in a very low concentrations of the neurotransmitter in the synaptic cleft at the site of the synaptic vesicle fusion (Shigemoto et al., 1996). The pyramidal neuron axon terminals expressing the $mGlu_7$ receptor were observed to predominantly form synapses with GABAergic interneurons (Shigemoto et al., 1996, 1997). Therefore, the final result of the pre-synaptic action of the activated mGlu7 receptor is the modulation of the postsynaptic GABAergic target interneuron [Fig.4 (1)]. This inhibition would cause the disinhibition of the other interneurons, targeting the glutamatergic network. Interestingly, $mGlu_7$ receptors are also expressed on some types of the interneuron population (e.g VIP positive) innervating $mGlu_{1\alpha}$-somatostatine postsynaptic interneurons [see: Fig.4 (2)] (Dalezios et al., 2002) and create a kind of GABA-GABA synaptic junction. The depression of the GABA release could lead to a disinhibition of postsynaptic interneuron and increased GABA release on their terminals [Fig.4 (3)], inhibiting the input zone to the pyramidal cells.

The pyramidal neurons expressing $mGlu_7$ on their terminals can form synapses with dendrites of the pyramidal cells in the prefrontal cortex (Samogyi et al., 2003). Therefore, AMN082, acting at presynaptic $mGlu_7$ receptors, may induce its antidepressant-like effect through the inhibition of the glutamate release [Fig. 4 (4)]. On the other hand, prefrontal pyramidal neurons have been shown as being inhibited by 5-HT via the activation of the inhibitory 5-HT_{1A} receptors [Fig.4 (5)] (Amargós-Bosch et al., 2004). Therefore, a selective blockade of 5-HT_{1A} receptors [Fig.4 (6)] may antagonize the inhibitory effects of 5-HT on pyramidal neurons, thus inducing an increased activity of these cells. This mechanism may account for a WAY100635-induced blockade of the antidepressant-like effect of AMN087 in the TST. This indicates that an interaction between group $mGlu_7$ receptors and 5-HT_{1A} receptors might be a general phenomenon involved in depression.

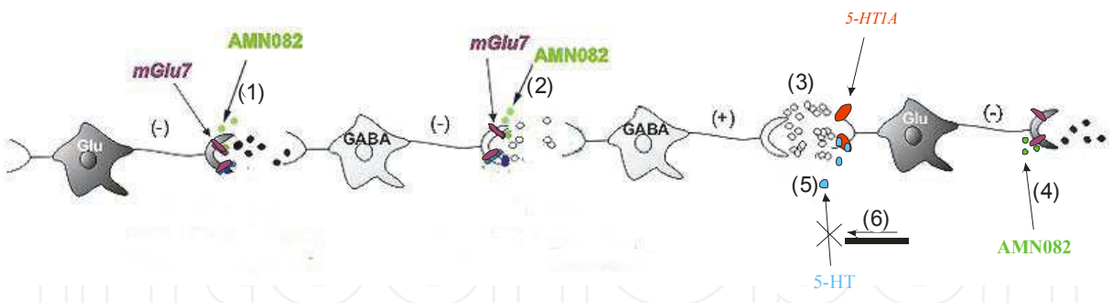


Fig. 4. Schematic representation of the mechanism of antidepressant-like action mediated by mGlu7 receptor positive allosteric modulator (see description in the text). Empty dots-GABA; black dots-Glu; (-)-inhibition; (+)-enhancement; the number of dots indicates the amount of neurotransmitter released

The mechanism of action of AMN082 involves not only GABAergic and glutamatergic neurotransmission. A major metabolite of the compound, Met-1, demonstrated a physiologically relevant transporter binding affinity at the serotonin transporter (SERT), dopamine transporter (DAT), and norepinephrine transporter (Sukoff Rizzo et al., 2011). Despite the involvement of the other mechanisms in the action of the $mGlu_7$ activator, the

modulation of the receptor is still crucial and, as in the studies with $mGlu_7$ KO mice the antidepressant-like action of the ligand was shown to be receptor specific (Cryan et al., 2003; Palucha et al., 2007).

4. The role of the GABAergic system in the treatment of depression

γ-aminobutyric acid (GABA) is the main inhibitory amino acid in the brain and constitutes nearly 40% of all neurotransmission. In the properly functioning brain it stays in the physiological balance with excitatory glutamate. The aberrations within this balance may lead to mental and neurological disorders that could be treated alternatively by influencing the glutamatergic or GABAergic neurotransmission (Linden & Schoepp, 2006). Glutamatergic receptors ligands have been discussed widely in the previous chapters. However, the role of GABA cannot be omitted, as it constitutes a natural opposite force for the glutamate. Therefore it may be speculated, that influencing the GABAergic neurotransmission may lead to the normalization of glutamatergic activity.

4.1 GABAergic theory of depression

The GABAergic theory of depression is relatively young when compared to monoaminergic theory, and was raised in the 1990s. The first rationale for considering GABA in depression was justified with mixed GABAmimetics, acting on both $GABA_A$ and $GABA_B$ receptors. The first successful clinical trials were obtained with progabide in 1978 (Bartholini et al., 1978). The effect of the drug was described as similar to standard antidepressants (Bartholini et al., 1978). Later on another GABAergic agent with similar efficacy as progabide, named fengabine, was also tested in double blind clinical studies, with positive results (Carpenter et al., 2006; Magni et al., 1989; Nielsen et al., 1990).

Both compound were also active in standard animal models of depression, such as olfactory bulbectomy or learned helplessness (Lloyd et al., 1987 a, b).

Biochemical studies confirmed the involvement of GABAergic mechanisms in mood disorders, as it was hypothesized that antidepressant drugs may act through increasing the GABAergic tone. The up-regulation of $GABA_B$ receptors appeared to be the fundamental facet of antidepressant drug action (Pilc &Lloyd, 1984). Parallel to these observations it was shown that the level of GABA was decreased in the plasma of depressed patients and the level of GAD67, enzyme synthesizing GABA from glutamate, was lowered in the brains of those patients. Recent studies confirmed the importance of both GABA receptors in depression, suggesting $GABA_B$ neurophysiological deficits to be related to the pathophysiology of major depressive disorder (Fatemi et al., 2005; Guidotti et al., 2000).

4.2 The role of the $GABA_A$ receptor in the mechanism of action of antidepressant drugs

The role of the $GABA_A$ receptor is evident in the field of anxiety disorders, and since the benzodiazepines, $GABA_A$ receptor positive modulators, are the mostly effective and the best known anxiolytic drugs. However as there is no convincing data that the drugs are effective in major depression yet, this issue will be not discussed here.

4.3 The role of the $GABA_B$ receptor in the mechanism of action of antidepressant drugs

The involvement of the $GABA_B$ receptor in depression and antidepressant-like therapy seems to be more important than the previously mentioned $GABA_A$ ionotropic channel. The first report on this subject was released in 1984 (Pilc & Lloyd, 1984). Later on several other papers appeared, and stated that antidepressant drugs of all classes as well as electroconvulsive therapy caused the up-regulation of the $GABA_B$ receptor in the hippocampus and frontal cortex (Gray and Green, 1987; Lloyd et al., 1985; Pratt et al., 1993). By contrast, the down regulation of the receptor was described in animal models of depression, in particular in the olfactory bulbectomy and learned helplessness. Concomitantly, the GABA release was also shown to be decreased in those animals. However, $GABA_B$ binding sites are not changed in the brains of depressed suicide victims, when measured in the frontal and temporal cortex, and in the hippocampus (Arranz et al., 1992; Cross et al., 1988).

It is commonly known that the $GABA_B$ receptor constitutes of two subunits ($GABA_{B1}$ and $GABA_{B2}$). The $GABA_{B1}$ subunit is further represented by two spice variants $GABA_{B1A}$ and $GABA_{B1B}$. More detailed studies concerning the influence of antidepressant drugs on the $GABA_B$ receptor complex revealed that those drugs selectively up-regulated the $GABA_{B1A}$ subunit in the hippocampus, having no effect on the other subunits (Sands et al., 2004). The elevation of $GABA_B$ receptors was also observed in the frontal cortex and spinal cord. Simultaneously the receptor affinity was not changed (Sands et al., 2004).

The existence of $GABA_B$ has been known since 1981 (Hill & Bowery, 1981), but the receptor was cloned relatively recently, in 1997, as the last receptor from the family of major neurotransmitters (Kaupman et al., 1997).

The first selective agonist of the $GABA_B$ receptor, baclofen, was shown to induce some antidepressant-like activities in animal models detecting the antidepressant-like activity of drugs, such as the olfactory bulbectomy (Delini-Stula & Vassout, 1978). The results were not confirmed in later studies, as no activity of baclofen was observed in the forced swim test nor behavioural despair test (Borsini et al., 1986). Moreover, the drug was shown to attenuate the effect of standard antidepressants, such as desipramine, mianserin or imipramine in some tests of antidepressant-like activity (Nakagawa et al. 1996a, b, c). The newer compounds potentiating the activity of GABA at the $GABA_B$ receptors (positive allosteric modulator) were shown not to display such an activity in the forced swim test or in the tail suspension test. The lack of this activity was observed for GS39783 and other $GABA_B$ positive allosteric modulators (Mombereau et al., 2004a, b; Slattery et al., 2005).

The synthesis of the high-affinity phosphinic acid-derived antagonist of the $GABA_B$ receptor opened a new window in terms of GABA and depression (Froestl et al., 2004). The ligands were shown to possess a great antidepressant-like potential in animal models of depression (see Table 5). The first studies concerned CGP36742 in a learned helplessness model of depression (Nakagawa et al., 1996 a,b,c, 1999).

Later on the second available antagonist, CGP51176 was shown to be active in the forced swim test (Bittiger et al., 1996; Nowak et al. 2006). Similar results were observed for other antagonists such as CGP56433A and CGP55845A (Slattery et al., 2005). Concomitantly the drugs had no effects on the spontaneous locomotor activity. These studies strongly support the notion about the antidepressant-like properties of $GABA_B$ receptor antagonists. The

Author	Compound/dose	Species	Test
Delini-Stula&Vassout, 1978	Baclofen (3-10mg/kg)	rats	Olfactory-bulb-ablation induced muricide
Nowak et al., 2006	CGP36742 (10-30mg/kg) CGP51176 (3-30mg/kg)	mice rats	Porsolt test Olfactory bulbectomy Chronic mild stress
Nakagawa et al., 1999	CGP36742 (30-100mg/kg)	rats	Learned helplessness
Slattery et al., 2005	CGP56433A (1-10mg/kg) CGP55845A (3-10mg/kg)	rats	Porsolt test
Bartholini et al., 1978; Magni et al., 1989; Nielsen et al., 1990	progabide, fengabide	human	Clinical study

Table 5. Collected data concerning the antidepressant-like activity of the $GABA_B$ receptor ligands.

studies keep in line with results obtained in the experiments with the use of $GABA_B$ knockout animals, as an antidepressant-like phenotype was observed in mice lacking either B1 or B2 subunit of $GABA_B$ receptor (Mombereau et al., 2004a, b, 2005).

In 2006 the paper of Nowak et al. (Nowak et al., 2006) further confirmed the above mentioned studies showing positive results with CGP51176 and CGP36742 in the chronic mild stress model of depression and in the olfactory bulbectomy model of depression. These activity was observed after chronic treatment, but not acute administration. Moreover, the chronic treatment with CGP51176 induced an increase in $GABA_B$ receptor binding, similar to how it was observed after standard antidepressant drugs (Nowak et al., 2006). Therefore, $GABA_B$ receptor seems to be an interesting target in the search of novel antidepressants.

The mechanism of action of $GABA_B$ ligands, especially $GABA_B$ antagonists, seems to also involve other neurotransmitters systems. The studies of Slattery et al. 2005 revealed that the pattern of action of CGP55845, the $GABA_B$ receptor antagonist, in the modified Porsolt swim test was similar to the one observed after selective serotonin reuptake inhibitors. This differed from tricyclic antidepressants because the drug decreased immobility time and increased swimming, having no activity on climbing behavior (Slattery et al., 2005). Concomitantly, the decrease in immobility elicited by CGP56433A was abolished after *p*CPA pretreatment, corresponding to an attenuation of the increase in swimming time (Slattery et al., 2005). As the pCPA pretreatment induces nearly 90% of serotonin depletion, it was evident that the action of the $GABA_B$ antagonist is serotonin-dependent.

The mechanism of the antidepressant-like action of those compounds is mechanistically different from the one described for anxiolytic effects (Wieronska et al., 2011), as the anxiolysis is mediated through the stimulation of $GABA_B$ receptor, confirming the dissociation of the role of the $GABA_B$ receptors in depression and anxiety (Mombereau et al., 2004, Pilc & Nowak, 2006), similar to how it was observed in the case of $mGlu_{2/3}$ receptors.

$GABA_B$ receptors are expressed on nerve endings of pyramidal neurons exerting the inhibitory effect on glutamatergic transmission (Forti et al., 1997; Samulack et al., 1993), therefore their blockade will cause an overflow of glutamate [Fig. 5 (1)] leading to stimulation of the inhibitory GABAergic neuron. On the other hand the blockade of GABAergic autoreceptors will also lead to inhibition of the target glutamatergic neuron [Fig. 5 (2)].

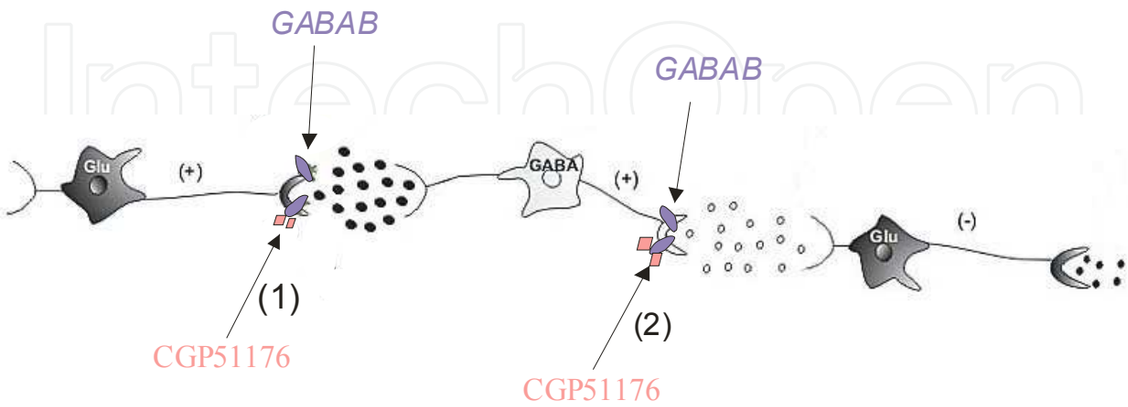


Fig. 5. Schematic representation of the mechanism of antidepressant-like action mediated by $GABA_B$ receptor antagonist(s) (see description in the text). empty dots- GABA; black dots- Glu; (-)-inhibition; (+)-enhancement; the number of dots indicates the amount of neurotransmitter released

Similar to the action of AMN082 described above, the antidepressant-like mechanism of action of $GABA_B$ antagonists occurs via an interaction with the serotonergic system (Slattery et al., 2005). However, determining the kind of receptors that are involved in the action of the compounds is still open for the investigations.

4.4 GABA receptors ligands and clinical studies

The clinical studies were started with progabide and fengabide, described earlier. As they were mixed $GABA_A/GABA_B$ mimetics, their action at particular receptor subtypes couldn't be estimated. More specific ligands acting at $GABA_B$ receptors were studied later on. The efficacy of $GABA_B$ antagonist, baclofen, and $GABA_A$ agonist, diazepam, was shown to be equal to amitryptiline in the treatment of affective disturbances in alcoholic patients (Krupitsky et al., 1993). Other studies showed that baclofen worsens the symptoms of depression (Post et al., 1991).

A study published in 2004 revealed the efficacy of SGS742 (CGP36742) in patients with mild cognitive impairment and opened the possibility for the compound to be investigated in humans (Froestl et al., 2004).

5. Conclusion

We described the mechanisms of the antidepressant-like efficacy of the ligands of metabotropic glutamatergic and GABAergic receptors in order to indicate, that the restoration of the GABA/Glu balance in the brain is an important part of their action. There are functional interactions between amino acids and monoamines (mainly serotonin), which

may account for the behavioral effects observed. The unique pharmacology of the metabotropic receptors, their localization in key circuits involved in the pathophysiology of depression, and the promise of the subtle modulation of glutamatergic and GABAergic neurotransmission by regulating the transmitter release and/or acting at the postsynaptic neurons make these receptors intriguing targets for the development of novel medication against depression. Our deliberations further reinforce the hypothesis of a disrupted excitatory/inhibitory balance in the pathophysiology of MDD and its restoration after successful antidepressant treatment.

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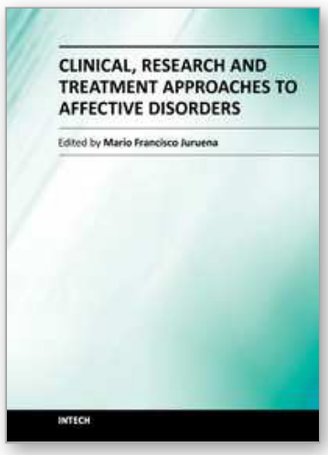
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The causes, development and outcomes of disorders are determined by the relationship of psychological, social and cultural factors with biochemistry and physiology. Biochemistry and physiology are not disconnected and different from the rest of our experiences and life events. This system is based on current studies that report that the brain and its cognitive processes show a fantastic synchronization. Written by the foremost experts on Affective Disorders worldwide, this book is characterized by its innovative, refreshing, and highly sensitive perspective on current knowledge of diagnostic, neurobiology, early life stress and treatment of Mood Disorders. The authors share a deep understanding of unique challenges and difficulties involved in Affective Disorders, and have achieved a balance among clinical, research and new treatment approaches to Affective Disorders. The chapters are written in a comprehensive, easily readable, and highly accessible style, stimulating readers, clinicians and researchers.

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Phone: +86-21-62489820
Fax: +86-21-62489821

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