BIOCHEMISTRY OF DEPRESSIVE DISORDERS. ROLE OF SEROTONIN, AMINO ACID NEUROTRANSMITTERS, SUBSTANCE P AND NEUROSTEROIDS

Alessandro Serretti, Paolo Olgiati

Abstract

The present paper reviews biochemical aspects of depression, focusing on abnormalities in: 1) serotonergic neurotransmission; 2) GABA and glutamate systems; 3) substance P; 4) neurosteroids. The results of literature search are discussed as regards their implications for the discovery of novel, more effective antidepressant treatments. Indeed, although depression is traditionally regarded as a treatable mental disorder, up to 50% of such patients may not have a satisfactory remission of symptoms after an adequate antidepressant treatment.

Declaration of Interest: None

Alessandro Serretti, M.D
Paolo Olgiati, M.D
Institute of Psychiatry, University of Bologna, Bologna, Italy

Corresponding Author
Alessandro Serretti, MD
Institute of Psychiatry, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy
Tel +39 051 6584233 Fax +39 051 521030
Email: alessandro.serretti@unibo.it

Introduction

Searching for the biological bases of depressive disorders has three levels of complexity. The first level concerns diagnostic classification. Current nosography, largely derived from Kraepelin's work, is based on a variety of syndromes characterized by phenomenologically heterogeneous manifestations (categories). This model, however, did not emerge as the best framework for biochemical research; hence, over the last two decades, a new approach has been developed, which consists of identifying clusters of similar signs and symptoms hypothesized to be pathophysiologically homogeneous (dimensions) and/or the use of endophenotypes. Such complexes are expected to warrant more reliable targets for psychotropic drugs, thus being preferential goals for biological investigations. A second level of complexity is linked to interactions among different neurotransmitters and circuitries supporting affective functions. Finally a third level stems from the view of depressive disorders as outcomes of physiological processes encompassing multiple steps, from neurotransmission to gene transcription. As a result studying their pathogenesis requires the involvement of a large number of disciplines; in particular, among those giving major contributions, chemistry, pharmacology, genetics and molecular biology.

1. Since the early 1980s, the widespread use of SSRI has established the key role of serotonin (5-HT) neurotransmission in the pathophysiology of depressive disorders. 5-HT is released by neurons located in the brainstem raphe. These cells are embedded in a variety of nuclei which form two distinct superior and inferior groups (Azmitia and Gannon 1986). The superior group comprises the caudal linear nucleus, dorsal raphe nucleus, median raphe nucleus, and supralemniscal nucleus and innervates diffusely the midbrain and forebrain. The inferior group consists of the nucleus raphe obscurus, nucleus raphe magnus, nucleus raphe pallidus and reticular nuclei that are sources of projections to the cerebellum, pons, medulla and spinal cord. The widespread innervation of the limbic system by serotonergic neurons is the basis for the influence of 5HT on affective processes and mood regulation.

2. Glutamate is the most important excitatory neurotransmitter in the brain. Glutamatergic

neurons project to noradrenergic nuclei in the locus coeruleus and serotonergic nuclei in the raphe (Ordway et al. 2002). Moreover the activity of dopaminergic neurons in the mesolimbic and mesocortical circuitries is also modulated by glutamate that excites dopamine neuron activity via ionotropic and metabotropic receptors.

3. GABA is the major inhibitory neurotransmitter of the brain, most highly concentrated in the substantia nigra and globus pallidus nuclei of the basal ganglia, the hypothalamus, the periaqueductal grey matter and the hippocampus. GABA provides inhibitory inputs to all monoamine nuclei (Olsen 2002). Due to its established interactions with the monoamine systems, GABA appears to be an ideal candidate for biological research on depression.

4. Substance P (SP) was identified in 1931 as a component of brain and intestinal extracts that had smooth muscle contractile activities (Santarelli et al. 2002b). SP belongs to a family of peptides that are termed neurokinins. SP has shown the highest affinity for the NK1 receptor, which is found in several brain areas that appear to be crucial for the regulation of affective behavior and response to stress such as the amygdala, hypothalamus, hippocampus and frontal cortex. In addition the NK1 receptor is localized to the raphe nuclei of the brainstem and locus coeruleus.

5. Over the past two decades it has become clear that steroid hormones can be synthesised in the brain by some of the same enzymes found in adrenals and gonads. These compounds have been termed neurosteroids and their physiological properties have been progressively elucidated. (Stoffel-Wagner 2001). Involvement in neuropsychiatric disorders has been firmly established for dehydroepiandrosterone (DHEA), 3alpha-5alpha-tetrahydrodeoxycorticosterone (3alpha-5alpha-THDOC) and 3alpha-hydroxysteroid-5alpha-pregnan-20-one (allopregnanolone). Allopregnanolone and more recently THDOC have been displayed to act as positive modulators of the GABA-A receptor function thereby regulating complex emotional states such as anxiety and depression (Van Broekhoven and Verkes 2003).

This paper will review recent discoveries on the role of serotonin neurotransmission, excitatory (glutamate) and inhibitory (GABA) amino acids, neurokinins and neurosteroids in the pathophysiology of depression. The findings are discussed as regards their implications for treatment of depressive disorders

Methods

Data were retrieved from in vitro and in vivo studies, searchable from PubMed. Publication time was until August 2008. The following key words were used for literature search: depression; 5-HT1a; 5-HT2a; 5HTTLPR; tryptophan hydroxylase; glutamate; NMDA receptor; AMPA receptor; substance P; neurokinin; NK1; neurosteroid; antidepressant.

Results

Serotonin system

Four components of the serotonin system have been implicated in the pathophysiology of depression:

5-HT1a receptor

Presynaptic 5HT1a receptors are present on the soma and dendrites of serotonergic neurons (autoreceptors). Their physiological properties have been extensively investigated (Blier and de Montigny 1987). When activated they slow down neural firing activity thereby inhibiting serotonin release. This effect is more prominent in 5HT cells originating from the dorsal raphe. With treatment prolongation neurons recover their normal firing rate as a result of 5HT1a autoreceptor desensitisation. Such findings led to speculate that delay in response to antidepressant drugs might be attributable to transient 5HT1a autoreceptor inhibitory control on serotonin release (Artigas et al. 1996). According to this hypothesis, blocking 5HT1a autoreceptors should hasten response to antidepressants. Thus, pindolol, a partial beta-adrenoceptor/5-HT1A receptor antagonist was first used to accelerate the onset of action of antidepressant drugs in 1994. Since then, it has been used in controlled trials to examine whether it can reduce the lag to clinical improvement, and/or to improve the clinical response in treatment-resistant patients. In 2004 a meta-analysis of nine RCTs comparing SSRIs plus pindolol vs SSRIs plus placebo favoured pindolol at 2 weeks time but not at four to 6 weeks (Ballesteros and Callado 2004). The acceleration of antidepressant response is more often reported with pindolol plus paroxetine, whereas no marked latency reduction has been shown with other SSRIs (Plenge and Mellerup 2003). Recently, in a double-blind trial of depressed patients treated with paroxetine, unipolar patients not previously treated and bipolar subjects, irrespective of previous treatments and duration of illness, demonstrated a significant benefit from pindolol augmentation (Geretsegger et al. 2008). Postsynaptic 5HT1a receptors are abundant in the hippocampus and limbic system. Their role in the pathobiology of depression is underscored by several lines of evidence. 5HT1a agonists such as the azapirone drugs are well known to exert anxiolytic and antidepressant effects and some of them showed efficacy in the treatment of major depression (Stahl et al. 1998). Postsynaptic 5HT1a receptors were found to be up-regulated by long term antidepressant treatments (Lund et al. 1992) and electroconvulsive therapy (Hayakawa et al. 1993). Notably these receptors are implicated in the phenomenon of neurogenesis, which occurs predominantly in the hippocampus and is supposed to be relevant for the clinical activity of antidepressant drugs (Gould 1999).

Recent studies using positron emission tomography confirm the involvement of 5-HT1a receptor in depression, though with contrasting results. Indeed some studies display an over expression of 5-HT1a receptors in drug-naive depressed patients (Parsey et al. 2006) while others demonstrate a

widespread reduction in 5-HT1a binding (Drevets et al. 2007, Hirvonen et al. 2008). Gender-specific alterations have been reported in cortical 5-HT1a receptor protein levels which were significantly decreased in the prefrontal cortex of depressed women but unchanged in male depressed subjects compared to gender-matched control subjects (Szewczyk et al. 2008). Conversely other studies report that women have significantly higher 5-HT1a receptor binding potentials than men in a wide array of cortical and subcortical brain regions, particularly in the hippocampus (Jovanovic et al. 2008). Further evidence supporting the role of 5-HT1a receptor in depression comes from genetic studies, which demonstrate the association of 5-HT1A gene polymorphisms with depressive disorder (Albert and Lemonde 2004, Anttila et al. 2007), suicidal behavior (Lemonde et al. 2003, Sawiniec et al. 2007) and antidepressant response (Kato et al. 2008, Lemonde et al. 2004, Levin et al. 2007, Serretti et al. 2004a, Yu et al. 2006).

A large body of evidence link 5-HT1a receptor to stress response, and therefore to environmental predisposition to depressive disorder. Behavioral models of stress in animal, such as the forced swimming test and chronic mild test, have consistently demonstrated changes in postsynaptic 5HT1a receptor density in specific brain areas, decreases in dorsal raphe and hippocampus, increases in thalamus, hypothalamus and amygdala (Briones-Aranda et al. 2005). In rats exposure to aversive stimuli in the early postnatal period modifies responses to emotional stress in adult life via a 5-HT1a receptor-dependent mechanism (Matsumoto et al. 2005), and early life maternal separation alters 5-HT1a receptor densities in amygdaloid nuclei (Vicentic et al. 2006). Preclinical rodents models have revealed that variation in the gene encoding 5-HT1a receptor can affect serotonergic modulation of the acute response to stress and the adaptation to chronic stress (Holmes 2008). The activity of 5-HT cells in the dorsal raphe nuclei, as regulated by 5-HT1a autoreceptors, contributes to the formation and display of conditioned defeat (Cooper et al. 2008).

5-HT2a receptor

5HT2a receptors are located postsynaptically in the CNS and can also be found in platelets and other non CNS tissues. An increase in platelet 5HT2a binding sites was repeatedly demonstrated in depressed and suicidal patients, with some suggestion that increased binding in suicidal patients may be independent of a diagnosis of major depression (Pandey and Pandey 1990). Generally 5HT2a binding was thought to be a state marker although one recent study has suggested that it may not normalize with SSRI treatment (Schatzberg et al. 2002). Mixed results emerged from the study of 5HT2a binding in postmortem brain tissue, with some reports suggesting an increased binding in prefrontal cortex but others not (Schatzberg et al. 2002).

5HT2a brain activity can be analyzed in vivo with PET. Thus, a reduced 5HT2a activity in the right posterolateral frontal, orbitofrontal and anterior cingulate regions of depressed patients was found using the PET ligand F^{18} altanserin (Biver et al. 1997). In contrast another study reported no difference between suicidal depressives and controls using F^{18} seroperone (Meyer et al. 1999). PET was employed to study the effects of antidepressants on 5HT2a binding. Again results were inconsistent (Schatzberg et al. 2002). More recently, a correlation has emerged between increased 5-HT2a binding potential and higher scores on Dysfunctional Attitudes Scale, which supports the pathophysiological role of 5-HT2a receptor in a subgroup of depressed patients with high levels of dysfunctional attitude (Bhagwagar et al. 2006). In healthy subjects the personality dimension neuroticism and particularly its constituent trait, vulnerability, are positively associated with frontolimbic 5-HT2a binding. This points to a neurobiological link between personality risk factors for affective disorders and the serotonergic transmitter system and identify the serotonin 2A receptor as a biomarker for vulnerability to affective disorders (Frokjaer et al. 2008).

The T102C polymorphism of the 5-HT2a gene (HTR2A) was found to be involved in the development of depression by interacting with maternal nurturance (Jokela et al. 2007a). Variation in HTR2A is also associated with suicidality (Videtic et al. 2006) and outcome of antidepressant treatment (McMahon et al. 2006). Chronic treatment with SSRIs has been shown to induce desensitization of 5-HT2a receptor (Yamauchi et al. 2006). 5-HT2a antagonists have shown antidepressant properties in animal models (Patel et al. 2004, Wang 2005). The addition of 5-HT2a antagonists enhances the therapeutic effect of SSRIs (Marek et al. 2005).

Animal studies support the role of 5-HT2a receptor as a mediator of stress response. In the rabbit pretreatment with selective 5-HT2a antagonists was found to reduce head-bob behavior, an index of response to novelty stress (Aloyo and Dave 2007). Stress-induced learned helplessness has been used to explore the expression of 5-HT2a receptors in rat brains: exposure to single vs repeated stress resulted in different 5-HT2a receptor mRNA and protein expression in frontal cortex and hippocampus areas (Dwivedi et al. 2005). Overall the influence of 5-HT2a in psychiatric disorders seems quite relevant (Serretti et al. 2007a).

Tryptophan-hydroxylase

Tryptophan-hydroxylase (TPH) catalyses the rate-limiting step of serotonin biosynthesis. In humans TPH exists in two isoforms: TPH1, that is found in the pineal and gut, and TPH2, selectively expressed in the brain (Sakowski et al. 2006). TPH2 is more soluble than TPH1, has a higher molecular weight and different kinetic properties, including a lower catalytic efficiency towards phenylalanine (McKinney et al. 2005). TPH1 is expressed in the mouse brain during the late developmental stage, which suggests the involvement of this isoform in developmental predisposition to depressive disorder (Nakamura and Hasegawa 2007). Haplotype analysis has revealed that both TPH1 (Gizatullin et al. 2006, Sun et al. 2004) and TPH2 (Van Den Bogaert et al. 2006, Zill et al. 2004, Zhou et al. 2005) genes can confer susceptibility to major depression. The TPH1 gene has been found to mode-

rate the impact of social support on the onset of depressive symptoms in the general population (Jokela et al. 2007b) and, unlike TPH2, it exhibits association with stress-induced depression (Gizatullin et al. 2008). The A218C polymorphism of the TPH1 gene has been pointed to as a moderator of SSRI antidepressant response (Ham et al. 2007; Serretti et al. 2001a, 2001b), although its effect is not unequivocally demonstrated (Kato et al. 2007, Serretti et al. 2004b)

Serotonin transporter

Originally the serotonin transporter (SERT) was studied in platelets using tritiated-imipramine, and more recently with the higher affinity tritiate-paroxetine. There are numerous reports on decreased imipramine binding in the platelets of depressed patients as compared to healthy controls, and this difference was confirmed by a metaanalysis of seventy studies (Ellis and Salmond 1994).

Decrease in platelet 5HT uptake sites was once thought to be a trait marker of depression, that is, it did not appear to be modifiable by treatment. Further research, however, has revealed that this finding does normalize with treatment, but it is necessary to wait for sufficient periods to allow for protein regeneration (Nemeroff et al. 1994).

The serotonin transporter was also examined in postmortem brain tissue. Early studies in this area pointed to decreased SERT binding in suicide brains but this result has not been replicated in more recent works (Schatzberg et al. 2002).

The development of SPECT ligands that bind selectively to the serotonin transporter allowed in vivo study in humans. In one study, a significant difference in SERT binding was observed between depressed patients and controls (Malison et al. 1998). Recently, research focus has become SERT binding in untreated depressives and changes following antidepressant treatment. A subgroup of depressed patients are characterized by reduced SERT binding potential in several brain regions involved in mood regulation and affectivity (amygdala; anterior cingulate cortex; hippocampus; thalamus; dorsal raphe). These patients are often non-remitters after antidepressant treatment. Conversely remitters do not differ from healthy controls in SERT expression (Bhagwagar et al. 2007a, Miller et al. 2008). In seasonal affective disorder studies indicate that SERT is in a hyperfunctional state during depression and normalizes after light therapy or in natural remission (Willeit et al. 2008). In serotonergic neurons exposure to citalopram causes an internalization of SERT proteins from the cell surface and induces a redistribution of SERT from neurite extensions into the soma. This process is reversible on drug removal. Antidepressant treatment does not alter SERT mRNA expression, suggesting that SERT trafficking from and to the cell membrane is regulated on the posttranscriptional level (Lau et al. 2008).

A polymorphism in the promoter region of the SERT gene (5-HTTLPR or SLC6A4) has been associated with outcome of antidepressant treatment. The s-allele could predict a worse response to antidepressant drugs in depressed patients of Caucasian origin (Serretti et al. 2007b). The same polymorphism has emerged as a susceptibility factor for affective disorders (Lotrich and Pollock 2004) and a marker of depression and anxiety-related personality traits (Dragan and Oniszczenko 2006, Sen et al. 2004). In 2003 Caspi was the first to demonstrate that individuals with one or two copies of the 5-HTTLPR s-allele exhibited more depressive symptoms, diagnosable depression and suicidality in relation to stressful live-events compared to subjects homozygous for the l-allele (Caspi et al. 2003). Gillespie et al. suggested that this gene x environment interaction might be specific to young people (Gillespie et al. 2005). Gender is another critical variable. Males and women carrying the short 5-HTTLPR allele react to different kinds of environmental factors: males are affected by living with separated parents, females by traumatic conflicts within the family. The s-allele has negative consequences for females, among whom it leads to develop depressive symptoms, whereas males seem to be protected from depression (Sjoberg et al. 2006). In 5-HTTLPR genotyped subjects the risk for depression is modifiable by positive or negative characteristics of the environment: s/s homozigosity is associated with greater depressive symptomatology in individuals with a stressful early family environment or recent stressful life-events; instead less depressive symptoms are reported in subjects with a supportive family environment or recent positive experiences (Taylor et al. 2006). Overall 5-HTTLPR variants have a very broad, though small, effect on many aspects of human behavior, as reviewed elsewhere (Serretti et al. 2006).

Gamma-Amino-Butyric-Acid

GABA is synthesised by a specific enzyme, termed L-glutamic acid decarboxylase (GAD), in one step from its precursor L-glutamate, which is known to be itself a neurotransmitter. Much of glutamate and GABA in the CNS is derived from glial storage pools of glutamine (Olsen 2002). Two genes for GAD have been cloned, and the two forms of the enzyme are proposed to differ in their affinity for the cofactor pyridoxal phosphate and the subcellular localization (Erlander and Tobin 1991). Three types of GABA receptors have been identified to date. $GABA_A$ receptors are ligand-gated chloride channels which can produce rapid, less than 100 msec, inhibitory postsynaptic potentials (Olsen and Tobin 1990). $GABA_B$ receptors are coupled with GTP binding proteins and promote slow postsynaptic inhibition (Bowery 1993). Recently a new $GABA_C$ subtype has been found. It is a chloride channel receptor which, unlike $GABA_A$, is insensitive to bicuculline and cannot be modified by benzodiazepines and anesthetics (Johnston 1997).

GABA hypofunction in animal studies

Rodent studies evidence decreased GABA concentrations and receptor function in several brain regions in response to both acute and chronic stress (Acosta et al. 1993, Borsini et al. 1988). Moreover GABA agonists prevent and reverse inhibited behaviors

in rodent models of depression whereas GABA antagonists produce such behaviors (Brambilla et al. 2003, Petty and Sherman 1981).

GABA levels in humans

Some studies indicate lower CSF GABA levels in patients with major depression than healthy controls, although this finding is not confirmed by the whole literature (Gold et al. 1980, Roy et al. 1991). Plasma GABA concentrations are lower in unipolar depressives and may not normalize with treatment (Berretini et al. 1983, Petty et al. 1992). In refractory depressed patients undergoing cingulotomy, GABA levels are inversely related to degree of depression (Honig et al. 1989).

Proton magnetic resonance (RM) spectroscopy enables the direct measurement of brain GABA through a non invasive procedure. This technique has allowed to demonstrate significantly decreased GABA levels in the occipital cortex of depressed patients as compared with healthy controls (Sanacora et al. 1999). The original finding was replicated in subsequent studies which analyzed medication-free recovered unipolar depressed and bipolar subjects (Bhagwagar et al. 2007b, Bhagwagar et al. 2008). GABA concentrations were found to increase following a course of ECT (Sanacora et al. 2003) and after therapy with SSRI drugs (Sanacora et al. 2002). Conversely cognitive behavioral therapy has a less robust effect on cortical GABA content (Sanacora et al. 2006).

Presynaptic GAD and GABA-T

Prior studies on presynaptic GAD and GABA transaminase (GABA-T) demonstrated unchanged activity and levels in suicide victims (Cheetham et al. 1988, Sherif et al. 1991). Recently, the quantitative analysis of GAD in the brain of suicide victims has revealed significant decreases in areas such as the hippocampus, the prefrontal cortex and the orbitofrontal cortex, with differences between major depressive disorder and bipolar disorder (Bielau et al. 2007, Gos et al. 2008). Such findings, however, are difficult to interpret since the activity of GAD is known be reduced by protracted terminal diseases (McGeer and McGeer 1976) and GABA-T is not specifically localized in GABA neurons (Nagai et al. 1983). Thus GABA uptake sites seem to be more reliable markers of GABAergic function. In a previous work, the binding of nipecotic acid to GABA uptake sites was found to be decreased in the frontal cortex of suicide victims compared with controls, although the difference was not statistically significant (Sundman et al. 1997). These results were not replicated in a subsequent study with tiagabine, a compound that binds selectively to GABA transportesr – 1 (GAT-1), which is predominantly located on GABAergic neurons (Sundman-Eriksson and Allard 2002).

Role of GABA in stress response

Stress-induced alterations in various components of the GABA system have been described since the 1980s (Biggio et al. 1984, Fride et al. 1985, Havoundjian et al. 1986, Otero Losada 1988, Yoneda et al. 1983). In the last decade, many studies have better elucidated the role of GABA in response to stress. In rats restraint exposure was associated with reduced GABAergic neurotransmission in the amygdala and frontal cortex (Martijena et al. 2002); additionally, juvenile stress resulted in an immature-like expression profile of GABA-A receptor subunits (Jacobson-Pick et al. 2008). Social defeat stress, induced in mice by exposure to aggression, alters cannabinoid receptor-mediated control of GABAergic transmission in the striatum (Rossi et al. 2008).

Mice with heterozygous deletion of the gamma2 subunit of GABA-A receptor were found to exhibit heightened behavioral inhibition to naturally aversive situations and a behavioral phenotype that is considered to be indicative of anxiety. In addition these animals were characterized by reduced adult hippocampal neurogenesis (Earnheart et al. 2007).
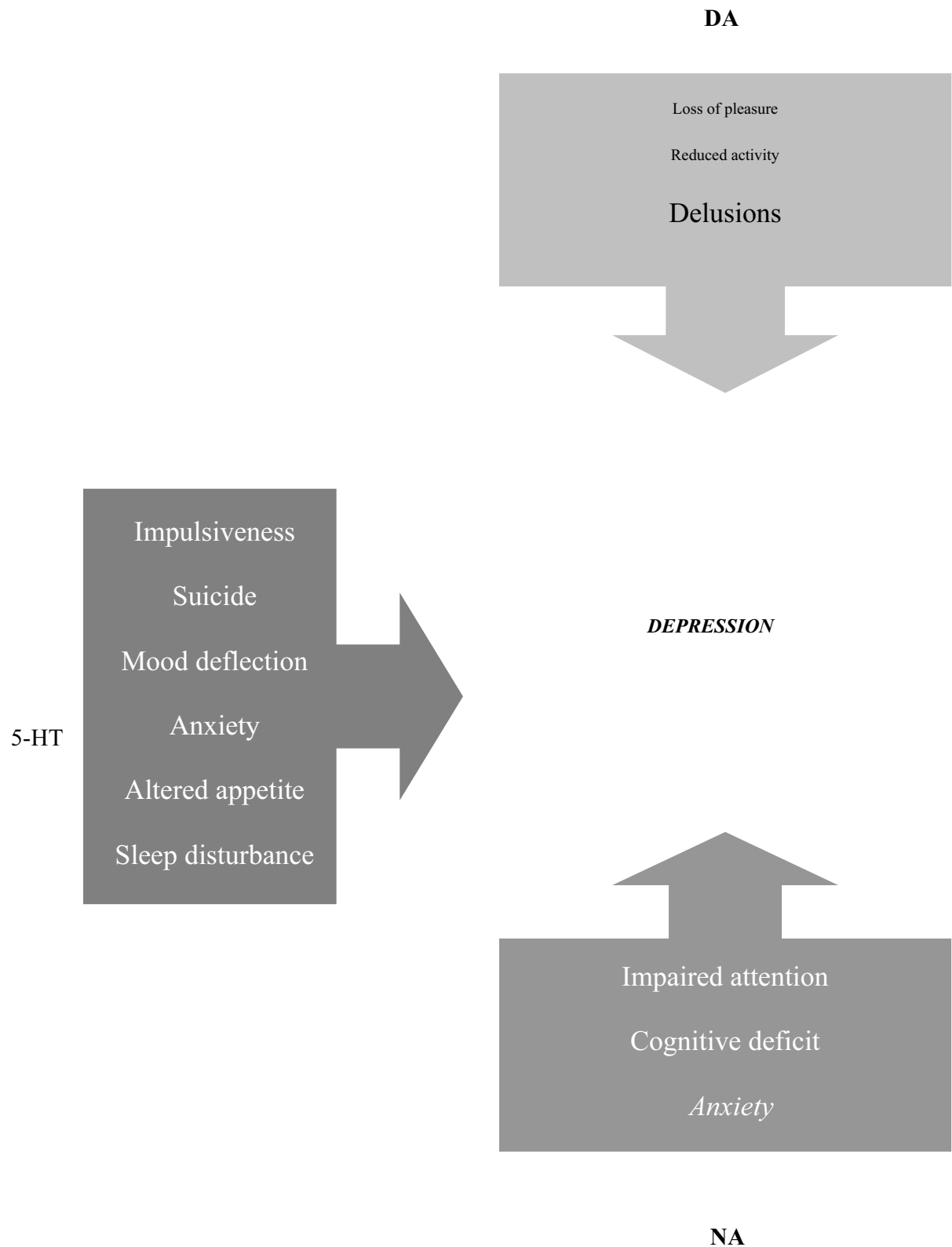
GLUTAMIC ACID

Glutamate is formed mainly from the Krebbs cycle intermediate, oxoglutarate, by the action of GABA aminotransferase. There are three main glutamate receptor subtypes: NMDA, AMPA/Kainate and metabotropic.

NMDA and AMPA/kainate receptors are directly coupled to cation channels whereas metabotropic receptors act through intracellular second messengers. The channels controlled by NMDA receptors are highly permeant to calcium and can be blocked by magnesium. They mediate slower excitatory responses and, through their effects on calcium entry, are involved in long-term potentiation and play a complex role in controlling neuronal plasticity. Furthermore excessive calcium entry produced by NMDA-receptor activation can result in excitotoxicity and ultimately in neuron death. On the contrary AMPA/kainate receptors are characterized by low permeability to calcium and appear to be involved in fast excitatory transmission. Finally metabotropic receptors are coupled with G-proteins that activate the IP3/DAG transduction pathway. Their physiological role is quite obscure although they have recently been implicated in excitotoxicity as well.
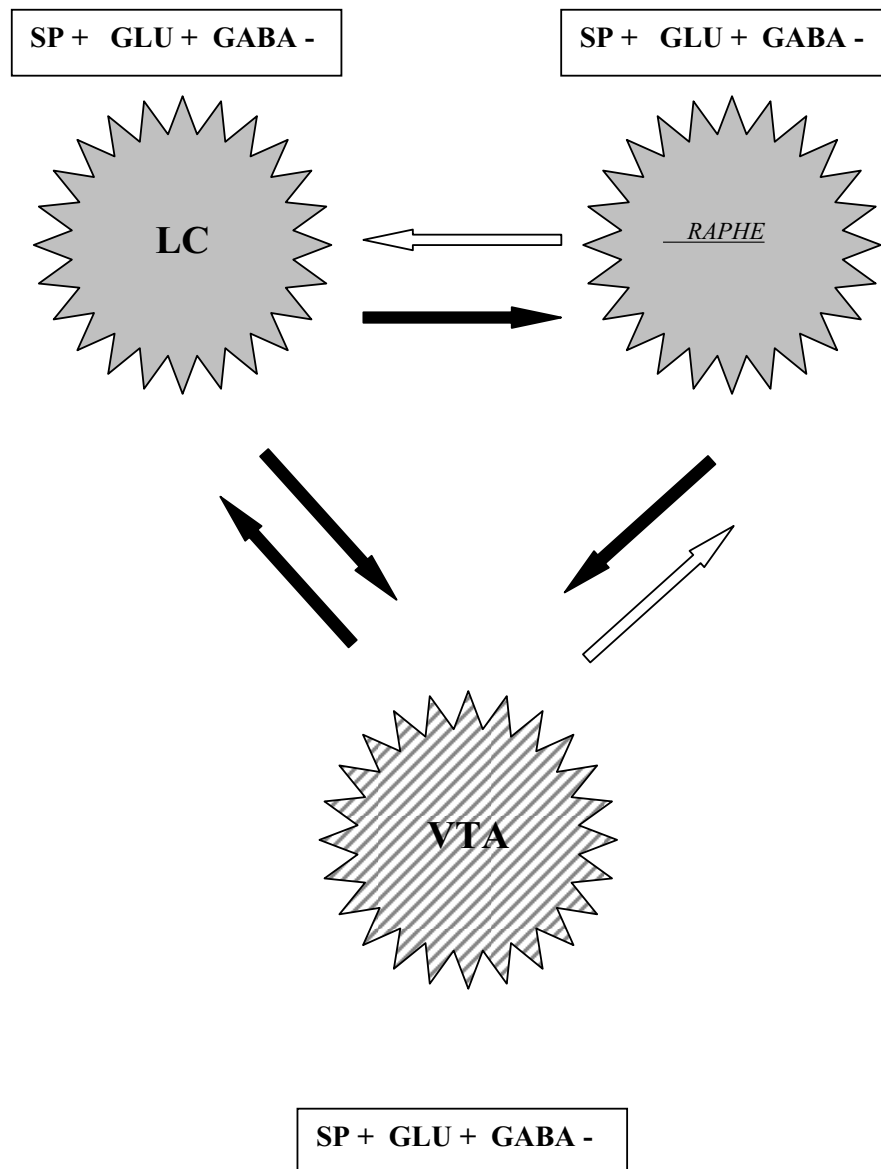
Hyperglutamatergic hypothesis of depression

NMDA receptor antagonists were shown to have antidepressant actions in animal models of depression (Paul 1997) and humans (Berman et al. 2000). High levels of serum glutamate were reported in depressed patients, though with exceptions (Altamura et al. 1995, Altamura et al. 1993). In addition there are studies that suggest alterations in the allosterism of NMDA receptor binding in the frontal cortex of suicide victims (Nowak et al. 1995) as well as elevated levels of CSF glutamine in depressed patients (Levine et al. 2000). Such findings have led to the speculation that there may be excessive glutamate neurotransmission in depressive disorders. However this hypothesis is not confirmed by the whole evidence from the literature.

Figure 1. *Neurotransmitters and symptoms of depression*

DA

Loss of pleasure

Reduced activity

Delusions

Impulsiveness

Suicide

Mood deflection

Anxiety

Altered appetite

Sleep disturbance

5-HT

DEPRESSION

Impaired attention

Cognitive deficit

Anxiety

NA

Figure 2. *Intrinsic and extrinsic regulation of monoamine systems*

Black arrow and + : excitatory effect

White arrow and - : inhibitory effect

RM spectroscopy has been used to detect glutamate levels in vivo. This method allowed to demonstrate a significant decrease in glutamate concentrations in the anterior cingulate cortex of major depressive patients (Auer et al. 2000). Similarly, anterior cingulate glutamate levels were found to be reduced in children and adolescents with major depressive disorder. This reduction was associated with increased severity of functional impairment (Mirza et al. 2004). On the contrary a subsequent study reported higher levels of glutamate/glutamine in depressed geriatric patients than in controls (Binesh et al. 2004).

Function of AMPA and NMDA receptors

Such contrasting results emerging from RM spectroscopy studies suggest that it may be necessary to reconsider the role of the glutamate system in depression. The revised glutamatergic hypothesis is centered around the different function of AMPA and NMDA receptors.

Compounds which augment signaling through AMPA receptors exhibit antidepressant-like behavioral effects in animal models (Bleakman et al. 2007), and produce neuronal effects similar to those observed with currently available antidepressants, including neurotrophin induction (BDNF) and increases in hippocampal progenitor cell proliferation (Alt et al. 2006). Similar antidepressant effects have been reported with NMDA receptor antagonists such as ketamine (Berman et al. 2000, Garcia et al. 2008, Maeng and Zarate 2007). Thus AMPA receptor hypofunction and NMDA receptor hyperactivity are two possible mechanisms underlying depressive states. Recent data indicate that these alterations are interrelated. Indeed mice with deletion of the main AMPA receptor subunit GluR-A have been characterized by a "depressive" phenotype including learned helplessness, decreased serotonin and norepinephrine levels, and disturbed glutamate homeostasis with increased glutamate levels and increased NMDA receptor expression (Chourbaji et al. 2008). Notably, the antidepressant-like effects of NMDA receptor antagonists appear to be mediated by increased AMPA-to-NMDA glutamate receptor throughput, as such effects are attenuated by pre-treatment with AMPA receptor antagonists (Maeng et al. 2008).

Neurotoxicity and response to stress

Atrophy of as much as approximately 20% of hippocampal volume is demonstrable in depressives after controlling for total brain volume or volume of amygdala and temporal lobe. Such an atrophy has been found to increase with longer durations of depression and it persists up to decades after depressions have resolved (Bremner et al. 2000). This phenomenon might be related to chronic stress (McEwen and Magarinos 1997). A large body of evidence indicate that the deleterious modifications induced in the hippocampus by stress involve a decrease in neurotrophic factors (e.g BDNF) following glutamate NMDA receptor activation (Joca et al. 2007).

Recently, AMPA receptor has also been recognized to play a substantial role in stress response. Exposure to chronic mild stress is known to induce anhedonia in adult animals. This effect has been associated in an age-dependent manner with decreased neurogenesis and BDNF levels in the hippocampus, and altered hippocampal expression of AMPA receptor GluR1 subunit (Toth et al. 2008).

Substance P

Early experiments with localised application of SP or NK1 receptor agonists demonstrated potentiation of anxiety-like behaviors in several animal models (Elliott 1988). Additionally, exposure of animals to stress has been associated with changes in endogenous SP (Bannon et al. 1986), whereas antidepressant and anxiolytic drugs have been shown to reduce SP synthesis (Shirayama et al. 1996). In the clinical setting, elevated SP levels have been reported in the CSF (Rimon et al. 1984) and serum (Herpfer and Lieb 2003) of depressed patients, although negative replications were also described (Berrettini et al. 1985). Yet most evidence about the behavioral effects of SP derives from knockout studies. NK1 -/- mice (lacking the NK1 receptor gene) have been compared with control (wild-type) mice in a variety of animal models including the elevated maze plus (EMP), novelty suppressed feeding (NSF), forced swimming (FS) and open field (OF) test (Santarelli et al. 2002a). In all these assays NK1-/- mice exhibited an attenuation of anxiety- and depression-like behaviors which is consistent with disruption in the NK1-SP pathway being a putative mechanism underlying anxiety and depression.

Interactions between SP and monoamine pathways

There is increasing evidence that SP may induce depressive states by inhibiting serotonin neuro-transmission. For example, the firing rate of 5HT neurons in the dorsal raphe (DR) has been reported to be higher in NKI receptor knockout mice compared with wild-type mice (Santarelli et al. 2002a). Little is known about physiological mechanisms underlying this effect of SP, however recent studies emphasize interactions with presynaptic 5HT1a autoreceptors. Accordingly, the inhibition of 5HT neuron firing which follows administration of 5HT1a agonists has been found markedly reduced in NK1 knockout mice (Santarelli et al. 2002a). In the frontal cortex of mice, genetic or pharmacological inactivation of 5-HT1A autoreceptors has been shown to block increase in 5-HTT levels following intraraphe SP injection (Guiard et al. 2007). An indirect mechanism has also been proposed. Indeed abundant NK1 receptors have been observed in the LC (Santarelli et al. 2002b). This finding, together with noradrenergic inputs stimulating serotonergic activity in the DR, suggests that SP might inhibit noradrenergic neurotransmission, which in turn would cause reduction in 5HT cell firing. This process might primarily involve a2-adrenoceptors. Consistent with this hypothesis, SP antagonists have been demonstrated to attenuate the

inhibition of NE and 5HT neuronal firing in response to administration of a2-adrenoceptor agonist clonidine (Santarelli et al. 2002a).

Antidepressant effects of NK1 receptor antagonists

In animals, pharmacological blockade of NK1 receptors attenuates anxiety- and depression- like behaviors (Rupniak et al. 2000) as well as the effect of chronic stress in models of depression (van der Hart et al. 2005). These preclinical data indicate a possible use of SP antagonists (SPAs) as antidepressant agents. Thus a number of authors have reported on clinical experiences with SPAs in depressed patients (Ranga and Krishnan 2002). Aprepitant, which interacts selectively with human NK1 receptors, was the first SPA to be tested in the treatment of depression. A phase 2 trial showed similar decrease in HAM-D$_{17}$ scores with aprepitant and paroxetine, both superior to placebo. Aprepitant, however, appeared to be particularly effective on anxious manifestations. Subsequently another SPA became available for clinical evaluation. Similar to aprepitant this agent, termed "compound A", is characterized by high oral bioavailability and cerebral penetration, as well as high selectivity and affinity for the NK1 receptor. In a phase 2 trial compound A provided significantly greater improvement in HAM-D$_{17}$ scores than placebo. Such reductions in depressive symptoms were even more prominent than those reported in the previous study with aprepitant.

Neurosteroids

Plasma and CSF concentrations of allo-pregnanolone appear decreased in depressed patients and normalize following effective psychophar-macological treatment. This phenomenon was first observed in subjects receiving SSRIs and subsequently extended to other classes of antidepressants (Nechmad et al. 2003, Van Broekhoven and Verkes 2003).

Several findings support the antidepressant activity of allopregnanolone. These include an antidepressant effect demonstrated in animal models of depression and a suppressing effect on CRH and arginine-vasopressin (AVP) gene expression (Nin et al. 2008, Van Broekhoven and Verkes 2003). Although the role of THDOC within the brain is still unclear, there is evidence that stress increases this steroid to levels that activate GABA A receptors. This might represent a compensatory mechanism aiming to control anxiety (Reddy 2003). Also DHEA seems to have a beneficial activity in depression possibly as a result of its sigma 1 receptor- mediated stimulation of serotonin and norepinephrine transmission as well as its anti-glucocorticoid and cognition enhancing effects (Van Broekhoven and Verkes 2003). GABAergic neuro-transmission in the mesolimbic system and sigma-1 receptor have also been pointed to as mediators of the antidepressant effects of neurosteroids (Dhir and Kulkarni 2008, Genud et al. 2008).

Discussion

Although depression is traditionally considered a treatable mental disorder, up to 50% of such patients may not have a satisfactory response in spite of adequate trials of antidepressant drugs (Fava 2003). This emphasizes the need for novel, more effective antidepressant treatments. Accordingly, this paper analyzed possible candidates based on the biochemistry of depressive disorders. The serotonin system appears to play a substantial role in antidepressant response. 5-HT1a autoreceptors delay the onset of antidepressant response by inhibiting 5-HT cell firing (Artigas et al. 1996); nevertheless the efficacy of 5-HT1a antagonists such as pindolol in accelerating response to SSRIs is modest and principally involves paroxetine (Ballesteros and Callado 2004, Plenge and Mellerup 2003). Although 5-HT1a binding in depressive disorders has shown inconsistent findings (Drevets et al. 2007, Hirvonen et al. 2008, Parsey et al. 2006), pharmacogenetic studies reveal a significant influence of 5-HT1a receptor on antidepressant treatment outcome (Kato et al. 2008, Lemonde et al. 2004, Serretti et al. 2004a). Additionally, this receptor is targeted by antidepressant drugs such as buspirone. Therefore, further research is warranted to elucidate the involvement of 5-HT1a receptor in antidepressant response and other aspects of mood disorders (Drago et al. 2007).

5-HT2a receptor binding is reported to be increased, unchanged or decreased in depression and suicide (Bhagwagar et al. 2006, Biver et al. 1997, Meyer et al. 1999, Pandey and Pandey 1990, Schatzberg et al. 2002). Such inconsistent results leave the role of 5-HT2a receptor in depression unclear (Serretti et al. 2007a). However, antidepressant drugs and atypical antipsychotics with mood stabilizing properties are known to cause down-regulation of 5-HT2a receptors (Van Oekelen et al. 2003, Yamauchi et al. 2006). The HTR2A gene has been found to affect antidepressant treatment response (McMahon et al. 2006). 5-HT2a antagonists have emerged as potential novel antidepressant drugs. The antidepressant properties of these agents, so far demonstrated in animal models (Marek et al. 2005, Patel et al. 2004, Wang 2005), need to be confirmed by multi-center RCTs. Recently, a double-blind, placebo-controlled, parallel-group study demonstrated the efficacy of deramiclane, a potent and specific antagonist at serotonin 5-HT2a/2c receptor, in controlling the symptoms of generalyzed anxiety disorder (Naukkarinen et al. 2005).

Serotonin transporter is the site of action of various antidepressant classes (SSRIs; tricyclic; SNRIs). The 5-HTTLPR polymorphism in the promoter region of the serotonin transporter gene is probably the best documented genetic predictor of antidepressant treatment outcome, whose robust effect has been confirmed by a recent meta-analysis (Serretti et al. 2007b). The gene encoding TPH has also been associated with antidepressant response (Ham et al. 2007, Serretti et al. 2001a, Serretti et al. 2001b). However, pooling the effects of the two genes, approximately 25% of responders and 50% of nonresponders to SSRI treatment are not identifiable a priori (Serretti and Smeraldi 2004, Smits et al. 2007).

This appears to limit the contribution of serotonin transporter and tryptophan hydroxylase to the clinical activity of antidepressant drugs.

GABA levels are decreased in depression (Bhagwagar et al. 2007b, Bhagwagar et al. 2008, Sanacora et al. 1999). Consistent with a patho-physiological role of GABA neurotransmission, different antidepressant treatments share a common characteristic of increasing GABA concentrations (Sanacora et al. 2003, Sanacora et al. 2002). GABA agonists were found to reverse inhibited behaviors in rodent models of depression (Brambilla et al. 2003, Car and Wisniewska 2006, Gavioli et al. 2003). GABA(B) receptor antagonists have also shown antidepressant properties in rodents (Nowak et al. 2006). Such preclinical data need confirmation from clinical trials.

Ketamine, a potent NMDA antagonist, has emerged as a potential antidepressant agent in a small sample of patients with treatment-resistant major depression (Maeng and Zarate 2007). However ketamine is also an abuse substance. The perceptual and mood changes observed in those who have consumed ketamine are highly sensitive to age, dose, route of administration, previous experience and setting. At low doses, stimulant effects predominate and the effect of environmental conditions are significant; with higher doses, psychedelic effects predominate and the effect of the environment diminishes (Wolff and Winstock 2006). The potential of ketamine as a novel clinical tool is matched by its abuse potential outside medical settings, and by its enduring consequences. Indeed, if semantic memory impairments associated with recreational ketamine are reversible upon marked reduction of use, impairments to episodic memory and possibly attentional functioning appear long-lasting. In addition, schizotypal symptoms and perceptual distortions may persist after cessation of ketamine use (Morgan et al. 2004). The neuroprotective agent riluzole, that is currently in use to treat motoneuron disease, has been shown to inhibit NMDA receptor function probably via inhibition of protein kinase C (Lamanauskas and Nistri 2008). Two small studies revealed the efficacy of riluzole in treatment-resistant major depression (Zarate et al. 2004) and in the control of residual depressive symptoms (Sanacora et al. 2007). Anyway, the pooled sample included only twenty-nine subjects. Thus, these preliminary positive findings should be replicated in larger RCTs.

The antidepressant properties of NK1 antagonists, demonstrated in animal models of depression and in preliminary reports on depressed subjects (Rupniak et al. 2000), have prompted placebo-controlled trials in larger samples of major depression patients. Aprepitant and placebo were compared in five 8-week, double-blind trials, of which three also including a paroxetine group. Unlike paroxetine, that confirmed its antidepressant effect, aprepitant did not reveal any superiority to placebo (Keller et al. 2006). These findings suggest that the antidepressant effects of aprepitant, if present, are probably weaker than those of SSRI drugs. Conversely another NK1 antagonist, L-759274, has revealed antidepressant efficacy in a 6-week RCT of major depressed patients (Kramer et al. 2004). In summary, NK1 antagonists may be useful to treat depression, although their clinical efficacy needs to be determined.

Neurosteroids have been implied in the antidepressant and anxiolytic activity of SSRIs (Nechmad et al. 2003). Notably, changes in neurosteroid levels have been reported after antidepressant drug treatment but not after nonpharmacological therapy (Uzunova et al. 2006). However, the largest body of evidence comes from animal studies, clinical evidence is merely suggestive of a role of neuroactive steroids in the mechanism of action of clinically effective antidepressant therapy. Additional clinical studies evaluating the impact of successful pharmacological and nonpharmacological antidepressant therapies on changes in neuroactive steroid levels in both plasma and CSF samples of the same patients are necessary in order to more accurately address the relevance of 3alpha-reduced neuroactive steroids to major depressive disorder. Finally, proof-of-concept studies with drugs that are known to selectively elevate brain neurosteroid levels may offer a direct assessment of an involvement of neurosteroids in the treatment of depressive symptomatology.

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