Physiol. Res. 57: 151-164, 2008

MINIREVIEW

Neurobiological Aspects of Depressive Disorder and Antidepressant Treatment: Role of Glia

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Received March 30, 2006
Accepted February 22, 2007
On-line available April 25, 2007

Summary

Depression is a complex disorder related to chronic inflammatory processes, chronic stress changes and a hippocampal response. There is a increasing knowledge about the role of glial cells in nutrient supply to neurons, maintenance of synaptic contacts and tissue homeostasis within the CNS. Glial cells, viewed in the past as passive elements with a limited influence on neuronal function, are becoming recognized as active partners of neurons and are starting to be discussed as a possible therapeutic target. Their role in the pathogenesis of depressive disorders is also being reconsidered. Attention is devoted to studies of the different types of antidepressants and their effects on transmembrane signaling, including levels of α subunits of G proteins in C6 glioma cells *in vitro* as a model of postsynaptic changes *in vivo*. These models indicate similarities in antidepressant effects on G proteins of brain cells and effector cells of natural immunity, natural killers and granulocytes. Thus, an antidepressant response can exhibit certain common characteristics in functionally different systems which also participate in disease pathogenesis. There are, however, differences in the astrocyte G-protein responses to antidepressant treatment, indicating that antidepressants differ in their effect on glial signalization. Today mainstream approach to neurobiological basis of depressive disorders and other mood illnesses is linked to abnormalities in transmembrane signal transduction *via* G-protein coupled receptors. Intracellular signalization cascade modulation results in the activation of transcription factors with subsequent increased production of a wide array of products including growth factors and to changes in cellular activity and reactivity.

Key words

Major depression • Mood disorder • Antidepressant • Stress • Hippocampus • Neurogenesis • Astrocyte • C6 glioma cells • Immune system • Natural killer cells • Guanine-binding proteins • G proteins • Cell signal transduction

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Depression as a systemic disorder

Depression is one of the most prevalent mental disorders and one of leading causes of morbidity, mortality and economic burden worldwide. During four decades of research, biochemical research of depression has focused on the monoamine neurotransmitters and their receptors, in the past decade on receptor transduction mechanisms and intracellular signalization cascades (Avissar and Schreiber 2002, 2006). The family of G- proteins is a crucial convergence point in the signal transduction from many extracellular primary messengers to the intracellular second messengers and cell response (Kovářů and Kovářů 2005). G-protein measurement is applied as one of state markers of depressive patients or subjects under antidepressant, lithium or electro-convulsive treatment (Avissar and Schreiber 2002, 2006). Besides biochemical research, many other approaches contributed significantly to the understanding of

depression, one of the most fruitful contributions to this comprehension came from the field of psychoneuroimmunology and neuroimmunology (Haddad *et al.* 2002, Tafet and Bernardini 2003, Schiepers *et al*. 2005, Havrdová 2005).

Considerable evidence points to some similarities between depression and an inflammatory response (Leonard 2006). So-called "sickness behavior" which is phenomenologically similar to depression with fatigue, anhedonia, loss of energy and anorexia as the prominent features is linked to increased levels of pro-inflammatory cytokines such as IL-1, IL-6 or TNFα on the periphery, or within CNS (Kelley *et al*. 2003, Schiepers *et al*. 2005). Main producers of cytokins on the periphery are activated macrophages and T- and B-cells, in the CNS the activated microglial cells (Hauwel *et al*. 2005, Shiepers *et al*. 2005). Chronic inflammatory diseases, e.g. rheumatoid arthritis, are often accompanied by depression (Covic *et al*. 2006). Some of the immune system cells, e.g. granulocytes or natural killers, show during the course of depression and antidepressant treatment responses in many ways similar to the brain cells. Antidepressants affect cytokine production, promoting anti-inflammatory cytokine phenotype in human blood (Kovářů *et al*. 1997, Fišerová *et al.* 2002, Diamond *et al*. 2006).

Despite progressive understanding of systemic aspects of the depressive disorder, majority of authors are still considering depression as a primarily "brain disorder". There is growing knowledge on the role of glial cells in neurogenesis, neuronal development and maturation, nutrient supply, involvement in the communication at the synaptic contacts and tissue homeostasis and even active participation in the signalization processes (Araque *et al.* 1999, Laming *et al.* 2000, Hertz and Zielke 2004). Astrocytes are becoming recognized as active partners of neurons and there are several neuropsychiatric disorders where the role of astrocytes is recognized, e.g. Alzheimer´s disease, multiple sclerosis, HIV dementia or dementia with Lewy bodies.

The aim of this paper is to review astrocyte neurobiology associated with depression and antidepressant treatment within the frame of the systemic concept of depression. We will try to show astrocytes as a cell population, which can contribute to the depression development and is affecting neuronal functioning during the disease course. We will focus on the G-protein astrocytic signaling, in respect to the crucial role of G-proteins in the cell signal transduction. Antidepressant treatment is considered to exert its effect mainly on the neuronal population, we will try to demonstrate that astrocytes can already be regarded as one of the targets of antidepressant treatment which mediate a part of the beneficial effects.

Depression as a stress-induced selective neurodegeneration

Major depression involves disturbances in emotional, cognitive, immune, autonomic and endocrine functions (Nestler *et al*. 2002). Nervous, endocrine and immune systems share neurotransmitters, peptide hormones and cytokines as well as their receptors as a common chemical language to communicate with each other (Haddad *et al.* 2002, Fišerová *et al*. 2002, Tafet and Bernardini 2003, Kovářů and Kovářů 2005). This interplay is especially important during a stress response. Indeed stressful life events are often precipitating factors for the depression onset (Hayley *et al*. 2005, Sekot *et al*. 2005). Neurotransmitters alterations can affect functioning of these systems in many ways, for decades the depression has been linked particularly to disturbances in serotonergic and noradrenergic neurotransmission. Dysfunction in the neurotransmitter systems results, besides psychological and behavioral consequences, in the systemic effect with hyperactivation of stress hypothalamic-pituitary-adrenal axis (HPA) (Haddad *et al.* 2002, Tafet and Bernardini 2003). The resulting prolonged hypercortisolemia causes a wide array of organ and immune changes (Tafet and Bernardini 2003, Duman 2004, Gubba *et al*. 2004).

One of the most affected structures is the hippocampus which expresses high numbers of steroid receptors (Brown *et al.* 1999, Sheline *et al.* 2002). Hippocampus has a key role in declarative memory tasks and many other cognitive functions. It is also interconnected to the limbic system, participating in the recognition and regulation of emotional states as well as in the vegetative and autonomic function control, including HPA and sympathoadrenal system regulation (Sheline *et al.* 2002, Tafet and Bernardini 2003). Adrenal steroids modulate excitability of hippocampal neurons and interfere with the process of dendritic remodeling in CA3 hippocampal region, causing hippocampal dendritic atrophy (Brown *et al.* 1999, McEwen *et al.* 2002, Sheline *et al.* 2002, Hayley *et al*. 2005). Stress also impairs the process of adult neurogenesis, causing robust reduction in

the number of newly generated cells in the hippocampal dentatus gyrus within various stress paradigms (Czech *et al.* 2002, Duman 2004). Newly generated cells are functionally connected in the neuronal circuitry. Reduced adult neurogenesis is hypothesized to cause reduced ability of the hippocampus to cope with novelty and complex tasks leading to inadequate information processing at the interface systems involved in learning and affect regulation (Jakobs *et al.* 2000, Nestler *et al*. 2002, Kempermann *et al*. 2004, Doetsch and Hen 2005).

Today, mainstream therapy of depression *via* G-protein receptors and modulation of intracellular signalization cascade results in the activation of transcription factors, with subsequent increase of growth factor production; most notable are the studies of brain-derived growth factor (Duman and Monteggia 2006). This "neurotrophin hypothesis of depression" assumes that deficiency in the neurotrophin signalization systems with effects on cellular plasticity, viability and neurogenesis together with an enhancement of apoptotic processes caused by increased cortisol and pro-inflammatory cytokines levels play an important role in the depression etiopathogenesis (Aberg *et al*. 2000, Jacobs *et al.* 2000, Gould and Manji 2002, Nestler *et al*. 2002, Kempermann and Kronenberg 2003, Duman 2004, Duman and Monteggia 2006, Leonard 2006).

This is supported by the study of Alfonso *et al*. (2004) relating psychosocial stress and hippocampus response using model tree shrews. These authors screened two subtractive hippocampal cDNA libraries generated from RNA of cortisol-treated animals. Comparing transcript levels of stressed and control groups, four differences were demonstrated: nerve growth factor (NGF), membrane glycoprotein protein 6a (M6a), CDC-like kinase 1 (CLK-1), and α subunit of Gq protein (GNAQ) transcript levels were reduced by chronic psychosocial stress. All genes are related to neuronal differentiation, in agreement with previous findings of dendrite retraction and impairment of neurogenesis. Treatment by antidepressant clomipramine prevents these processes (with the exception of unchanged NGF). This study also supports the concept that stress and/or depressive disorders are accompanied by the neuronal dedifferentiation at least in the hippocampal area and antidepressants can prevent these processes (Alfonso *et al.* 2004).

Brain imaging studies show reductions of a hippocampal volume correlated with lifetime duration of depression (Steffens *et al.* 2000, Sheline *et al.* 2002). Reduction of the hippocampal volume is more prominent in depressive subjects exposed to trauma during childhood (Vithingham *et al*. 2002). Cell-counting studies have established that the major depressive disorder and bipolar illness are characterized by alterations in the density and size of neuronal and glial cells in fronto-limbic brain regions (Rajkowska 2003). There is a decrease in the neuronal and glial cell sizes and densities in the orbito-frontal regions and dorsolateral prefrontal cortexes of subjects with mood disorders and alcohol dependence, with more marked pathology of glial population (Miguel-Hidalgo and Rajkowska 2003). Reduced subgenual glial numbers are more prominent in subjects with the family history of depression (Öngür *et al*. 1998). There are also reduced numbers of glial cells and glial/neuronal ratio in the amygdala (Bowley *et al*. 2002) and reduced astrocytic marker GFAP in the cerebellum of subjects with mood disorders (Fatemi *et al*. 2004). Apoptosis is considered as a mechanism responsible for cell loss of both neurons and glia in the hippocampal region, requiring prolonged and severe stress exposure to occur (Tacuma *et al*. 2004, Lucassen *et al*. 2006)

These findings from histopathological and cell counting studies suggest that depression, as a complex disorder affecting many cell populations, also involves glial cells. In this review we will focus mainly on astrocytes and model C6 glioma (astrocytoma) cells, keeping in mind that contribution of other glial elements, e.g. oligodendrocytes or microglia, is also very important.

Astrocytes and etiopathogenesis of depression

Astrocytes are the prevailing glial cell population in the CNS, outnumbering neurons by a factor of 2-10, depending on the brain area (O´Kusky and Collonier 1982). They form a plexiform net of cells connected by gap junctions, providing thus a way for buffering extracellular ion dysbalances caused by neuronal activity (Syková 2005). Astroglial cells are an essential component of blood brain barrier, and provide nutrient supply to neurons (Laming *et al.* 2000). Astrocytes express virtually all neuronal neurotransmitter receptors, ion channels and neurotransmitter uptake sites (Table 1) (Hösli and Hösli 1993, Porter and McCarthy 1997, Deschepper 1998, Verkhratsky and Steinhäuser 2000, Nakagawa and Schwartz 2004). There is an intensive bidirectional communication between neurons

and glial cells at the synapses, a concept of ”gliotransmission” and “tripartite synapse“ was postulated where astrocytes are seen as active partners of neurons (Araque *et al.* 1999). Astrocytes participate in the neurotransmitter uptake from synaptic cleft, their synthesis from precursors, supply of neurotransmitter precursors to neuron and disposal of neurotransmitter excess (Danbolt 2001, Hertz and Zielke 2004). Released neurotransmitter can evoke Ca^{2+} concentration increases in astrocytes ensheathing the synaptic cleft which can signal back to the neuronal presynaptic terminal, and further increase or suppress the release of neurotransmitter (Cotrina *et al*. 2000, Parpura and Haydon 2000).

Astrocytes express both mineralocorticoid and glucocorticoid receptors, glucocorticoid levels regulate astrocytic reactivity and apoptosis, so that the downregulation of astrocytic growth factor production by glucocorticoids is demonstrated (Gubba *et al.* 2004). Glucocorticoids also inhibit glucose uptake by both astrocytes and neurons impairing thus complex brain energy metabolism (Horner *et al.* 1990).

Hippocampal atrophy observed in depression illness might be related to the altered excitatory amino acid system function. Excessive excitatory amino acid levels can be neurotoxic for neuronal terminals, neurons are in this respect greatly dependent on astrocyte clearance of elevated glutamate, because removal of glutamate is largely mediated by astrocytic transporters (Brown 1999, Danbolt 2001, Hertz and Zielke 2004). Elevated cAMP levels are demonstrated to enhance the expression of glutamate transporters (GLAST and GLT1) in rat astrocytes and regulate active calcium entry (Hughes *et al*. 2004, Pawlak *et al.* 2005). Growth factors, e.g. TGF-β and EGF, increase expression of glutamate transporters on astrocytes (Zelenaia *et al*. 2000). This can exert a protective effect in the endangered hippocampal structures, e.g. apical dendrites of pyramidal neurons in C3 area, enhance glutamate uptake and prevent excitatory amino acid-induced impairments of long-term potentiation and dendritic remodeling.

Astrocytes are important regulators of synapse numbers during development and in adulthood and are necessary for synapse maturation, proper receptor density and receptor subunit composition (Wilson *et al.* 1998, Donato 2001, Slezak and Pfrieger 2003). There is also evidence for astrocyte influence in the process of adult neurogenesis taking place in the subventricular and subgranular hippocampal zones (Seri *et al*. 2001, Nakayama *et al*. 2003, Hagg 2005). Interesting novel findings indicate glial gene *Ndrg2*, with putative roles in neuronal differentiation, synapse formation and axon-glial interactions regulated by glucocorticoids and

Table 1. Astrocyte receptors and membrane transporters.

Adrenergic β_2, β_1, α_1, $\alpha_{2A/D}$ receptors	Junker *et al*. 2002, Hösli and Hösli 1993, Porter *et al*. 1997
Serotonergic $5HT_{1A}$, $5\text{-}HT_{2A}$, $5HT_7$ receptors	Wilson *et al.* 1998, Barnes and Sharp 1999, Manev *et al.* 2001, Hannson *et al*. 1990
$GABA_A$, $GABA_{B1a}$, $GABA_{B1b}$, $GABA_{B2}$ receptors	Charles 2003, Porter *et al*. 1997
Glutamate AMPA/kainate, NMDA, mGLURs1, mGLURs5 receptors	Porter *et al*. 1997, Hertz and Zielke 2004
Purinergic P1, $P2X_1$, $P2X_1$, $P2Y_2$, $P2X_3$, $P2X_4$, $P2X_6$, $P2X_7$, $P2Y_2$, $P2Y_4$ receptors	Müller *et al.* 1995, Washburn and Neary 2006
Acetylcholine nicotinic receptors	Sharma and Vijayaraghavan 2001
Dopamine D_1, D_3, D_4, D_5 receptors	Ohta *et al*. 2003, Myiazaki *et al*. 2004
Serotonin transporter SERT	Fuller and Wong 1990, Bal *et al*. 1997, Inazu *et al*. 2001
Norepinephrine transporter NET, uptake 2 transporter	Inazu *et al*. 2003, Schildkraut and Money 2004
Glutamate transporters GLAST and GLT1	Danbolt 2001, Pawlak *et al.* 2005
Receptors for ńeurotrophic factors (NGF, BDNF, IGF, FGF, VEGR, EGFR, NT-3)	Müller *et al.* 1995, Hughes *et al*. 2004, Pawlak *et al.* 2005
Receptors for cytokines (CNTF, IL 1β, IL1ra, INF-γ, IL4, IL 6, IL10, TGFβ, TNFα)	Haddad *et al.* 2002, Nakagawa and Schwartz 2004
Peptide receptors for VIP, somatostatin, oxytocin, vasopressin, ANP, bradykin, thrombin	Deschepper 1998, Porter *et al.* 1997

antidepressants as a candidate for vulnerability gene to depression development (Nichols *et al*. 2005).

Following noxious insults associated with neuronal damage, astrocytes proliferate and change cell morphology, accumulation of cytoplasmic fibrillary material and profile of expressed receptors and adhesion molecules (Ridet *et al*. 1997, Sofroniew 2005). These reactive astrocytes produce neurotrophins, cytokines and chemokines which serve as mediators of the host defense system, inflammatory response and signals among astrocytes, neurons and microglia (Müller *et al.* 1995, Nakagawa and Schwartz 2004, Hauwel *et al*. 2005). Astrocytes are the main cell population, responsible for limiting inflammatory reactions within CNS, proinflammatory cytokines, prostaglandins and nitric oxide released during inflammatory response can attenuate the negative feedback and rise to the levels which can be deleterious for the neurons and other cells. For example, astrocytes lacking β_2-adrenoreceptors play a role in multiple sclerosis pathogenesis (De Keyser *et al*. 2004). There is a negative interference of inflammation with induction of long-term potentiation, neurite sprouting and neurogenesis in hippocampus (Vereker *et al*. 2001, Hayley *et al*. 2005). There is also an increase of apoptosis rate (Shiepers *et al*. 2005, Lucassen *et al*. 2006**).**

There is also an important involvement of astrocytes in serotonin metabolism. Depletion of serotonin precursor tryptophane in the diet is causing serotonin level reductions in the brain which is correlating with depressive symptomatology (Neumeister 2003, Leonard 2006). Tryptophane is metabolized by tryptophane hydroxylases to serotonin or alternatively by dioxygenases to kynurenine. Kynurenine is further metabolized to neurotoxic metabolites or neuroprotective kynurenic acid. Activity of dioxygenases is increased by cortisol and pro-inflammatory cytokines, e.g. IL-6 or INF-γ. Activated microglia is producing mostly neurotoxic metabolites 3-hydroxyanthranil acid and quinolinic acid, the main astrocyte metabolite is neuroprotective kynurenine (Guillemin *et al*. 2005). Astrocytes are also metabolizing quinolinic acid produced by the microglia, reducing thus neurotoxicity associated with microglial activation (Guillemin *et al*. 2001).

Reductions in neuronal size and density in certain areas observed in depression can be indicative of diminished glial ability to support full cell size and proper dendrite arborization. Given indispensable function of astrocytes in neuronal energy metabolism, reductions in the number of glial cells in the frontal lobes can participate in the lowered metabolism observed in these regions during a depressive episode. Astrocytes contain high levels of antioxidants and antioxidant enzymes. Reduced neuron supportive functions due to compromised astrocyte numbers or function can thus cause neurons to become more vulnerable to excessive corticosteroid mediated, excitotoxic glutamate, quinolinic acid or reactive oxygen species mediated damage (Drukarch *et al*. 1998, Brown *et al.* 1999, Brown 1999, Tacuma *et al*. 2004). Astrocyte-derived growth factors provide neuroprotection in various damage models (Junker *et al*. 2002, Nakagawa and Schwartz 2004, Tacuma *et al*. 2004). Astrocytes can further support neuronal viability by secretion of other neuroprotective factors and by restricting the inflammatory response and microglial activation (Müller *et al.* 1995, Villoslada and Genain 2004, Hauwel *et al*. 2005).

Effect of antidepressants on astrocytes

Several different classes of pharmacological agents are currently used for treatment of depression. These include monoamine oxidase inhibitors (MAO), nonselective inhibitors of monoamine uptake, tricyclic drugs e.g. imipramine, amitriptyline or desipramine, selective inhibitors of serotonin reuptake (SSRIs) like fluoxetine, sertraline or citalopram, inhibitors of noradrenaline reuptake and drugs inhibiting uptake of both monoamines, e.g. venlafaxine or milnacipran. Antidepressive effect proves also tianeptine which enhances uptake of monoamines on the synapses and is supposed to reverse stress-induced changes in the hippocampal formation and modulate glutamate receptors function (McEven *et al.* 2002). The main mechanism to terminate the action of synaptically released transmitters is the uptake by transporters which are present both on neurons and astrocytes (Fuller and Wong 1990, Bal *et al.* 1997, Inazu *et al*. 2001, 2003).

Norepinephrine transporter (NET) is sensitive to tricyclic drugs like desipramine and imipramine as well as to the mixed serotonin/noradrenaline uptake inhibitor milnacipram (Inazu *et al*. 2003). Elevation of norepinephrine levels by a blockade of uptake has a profound effect on astrocytic neurotransmitter receptor expression and cellular signalization cascade modulation. Astrocytes as a major cell population expressing β_1- and β_2-adrenoreceptors in the brain (Hösli and Hösli 1993)

are responding to antidepressant desipramine by decreasing the density of receptors (Sapena *et al*. 1996). Norepinephrine present in the synapse or other extraneuronal spaces can also be taken up into adjacent glia by a mechanism known as uptake 2, the extraneuronal monoamine transporter. This uptake 2 transporter is inhibited by formation of normetanephrine in glia by catechol O-methyltransferase from epinephrine. Thus astrocytes actively participate in an increase of synaptic norepinephrine and potentiate action of norepinephrine reuptake inhibitor antidepressants (Schildkraut and Mooney 2004).

Astrocytic serotonin sodium-dependent transporter SERT is sensitive to tricyclic drugs as well as to SSRIs and its expression is downregulated by SSRIs (Bal *et al.* 1997, Inazu *et al*. 2001, Benmansour *et a*l. 2002). Its expression and serotonin uptake are positively regulated by fibroblast growth factor (Kubota e*t al*. 2001). By binding to astrocytic $5HT_1$ receptors, serotonin stimulates production of neurotrophic S100β which is also produced after exposure to SSRI fluoxetine (Wilson *et al*. 1998, Donato 2001, Manev *et al.* 2001). The plasma level of S100β was significantly higher in patients with major depression and positively correlated with a response after 4 weeks of treatment (Arolt *et al*. 2003). Stimulation of $5\text{-}HT_{2A}$ receptors enhances the turnover of phosphoinositide and cAMP accumulation, there is a potentiation of β-adrenoreceptor stimulated accumulation of cAMP. Furthermore, in the presence of both noradrenaline and serotonin receptor agonists, the accumulation of cAMP is increased, and each of them alone can also cause cAMP accumulation (Hansson *et al*. 1990).

Influence of antidepressant treatment on glutamate system function is also studied. Tricyclic antidepressants when administered chronically have a modulatory effect on NMDA receptors; NMDA antagonist MK-801 produces a similar effect (Nowak *et al*. 1993). A stress-induced increase of glial glutamate transporter GLT-1a has also been demonstrated, while the administration of antidepressant tianeptine eliminates this effect, being concurrent with downregulation of NMDA-receptor subunits (McEwen *et al*. 2002).

With respect to the suspected neurotrophin shortage in depression, production of growth factors by astrocytes following antidepressant treatment was investigated. Chronic administration of antidepressants amitriptyline, clomipramine, mianserine, fluoxetine and paroxetine significantly increases glia-derived neurotrophic factor (GDNF) release from C6 glioma cells (Hisaoka *et al*. 2001). This GDNF release is further potentiated by serotonin (Hisaoka *et al*. 2004). Activation of β_2-adrenoreceptors by clenbuterol induced the synthesis of nerve growth factor (NGF), fibroblast growth factor (FGF) and transforming growth factor β1 (TGF β1) and provided neuroprotection against glutamate-induced and ischemic neuronal damage (Junker *et al*. 2002). Noradrenaline stimulates C6 glioma and cortical astrocytic cells to produce NGF *via* β-adrenergic receptor stimulation and adenylylcyclase activation (Stone and Ariano 1989).

Production of growth factors also seems to be regulated by dopamine D_1 and D_2 receptor agonists which may be required for NGF and glia-derived growth factor (GDGF) production by astrocytes (Ohta *et al*. 2003). Production of brain-derived neurotrophic factor by mouse astrocytes is also potentiated by dopaminergic stimulation (Inoue *et al*. 1997). MAO B inhibitor selegiline also stimulates growth factor (NGF, BDNF, and GDNF) production by mouse astrocytes (Mizuta *et a*l. 2000).

All monoamines (noradrenaline, serotonin or dopamine) are able to significantly increase BDNF astrocyte synthesis and secretion suggesting the existence of a positive reciprocal interaction between monoaminergic neuronal activity and astrocyte neurotrophic support in neuron-astrocyte crosstalk which has a dynamic role in mediating neuronal plasticity and trophic functions in the brain (Mojca-Juric *et al*. 2006).

Major depression and cell signaling

Biochemical approach to mood disorders and antidepressant action is based on monoamine theories describing lowered amounts of serotonin and norepinephrine in the synaptic cleft, and antidepressant influenced inhibition of the neurotransmitter reuptake into nerve terminals (Gould and Manji 2002, Avissar and Schreiber 2006). Attention is also focused on transmembrane signal transduction from neurotransmitter receptor coupled to heterotrimeric guanine-nucleotide binding proteins (G proteins), effector systems (enzymes, ion channels) and subsequent intracellular response.

Trimeric G proteins are composed of α, β and γ subunits. In the activated state especially G α subunits play a key role in transmembrane signaling from receptor-ligand complet (neurotransmitter, hormone, chemokine, etc.) to effector enzymes – adenylylcyclase ($G\ \alpha_s$, $G\ \alpha i_{1,2}$) and phospholipase C ($G\ \alpha_{q/11}$), producing second messengers cAMP and 1,4,5 inositoltriphosphate

(Spiegel 1996), respectively. Subsequent intracellular events predominantly regulate cascade of protein phosphorylation reactions by kinases. G proteins play a role in molecular switches in complex biological processes, such as synaptic plasticity, neuronal sprouting and cellular differentiation including early stages of neurogenesis, providing thus a mechanism for the epigenetic control of neuronal differentiation (Strubing *et al*. 1997, Avissar and Schreiber 2006).

Various studies are concerned with the involvement of G proteins in pathophysiology, diagnosis and treatment of mood disorders, modulation of G protein coupled neurotransmitter receptors and regulation of G protein function by arrestins, etc. (Gould and Manji, 2002, Avissar and Schreiber 2002, 2006). Furthermore, there was found an association between Gβ subunit expression or G protein β3 subunit gene polymorphism and antidepressant effect in major depression (Kovářů *et al*. 2001, Lee *et al*. 2004). Altered signal transduction components, especially α subunit of G protein expression and/or function, as well as changed mRNA levels were found in the postmortem brain tissue of patients with major depression and bipolar disorder (Young *et al*. 1993). Other studies revealed both G protein-influenced cAMP synthesis and G protein- induced activation of phosphoinositide signal transduction in postmortem brain cortex regions of suicide victims with major depression (Pacheco *et al*. 1996). In contrast, there is decreased phosphoinositide metabolism in postmortem brain samples of bipolar affective disorder subjects (Gonzales-Maeso *et al*. 2002).

In addition, the analyses of peripheral blood granulocytes or thrombocytes from depressive patients confirmed the relationship between alteration in G proteins and decreased G protein function in depression, and increased levels and the function of G proteins in bipolar disorder (Gould and Manji 2002, Avissar and Schreiber 2006). We demonstrated dynamic changes in levels of both G $\alpha_{q/11}$ and G α_s subunits of peripheral blood granulocytes of patients with unipolar depression during fluoxetine administration on days 3-28 (Kovářů *et al*. 2000, Kovářů and Kovářů 2005). Granulocytes are effectors of natural immunity likewise natural killer (NK) cells. Blunted peripheral blood NK cytotoxicity was demonstrated in major depression (Reynaert *et al*. 1995).

Antidepressants and cell signaling

Antidepressant effects during depressive disorders is based mainly on the inhibition of reuptake of biogenic amines – serotonin (5-HT), norepinephrine and/or dopamine into presynaptic nerve terminals (Gould and Manji 2002, Avissar and Schreiber 2006). Furthermore, antidepressants cause downregulation of β-adrenergic, 5-HT_1 and 5-HT_2 receptors at the postsynaptic level, when administered chronically. Decreased monoamine receptor densities following antidepressant treatment can also be seen in cell culture systems, such as C6 glioma cells lacking presynaptic input. Thus, monoamine receptor downregulation is directly resulting from postsynaptic action of the antidepressants. Reports concerning antidepressant postreceptor effects on G proteins involve both proximal effects on receptor coupled to G protein and distal effects on G protein-effector enzymes, adenylylcyclase and phospholipase C which are producing second messengers cAMP and 1,4,5-inositoltriphosphate.

Receptor-G protein coupled interactions are tightly regulated by mechanisms of desensitization, internalization, downregulation, and resensitization which are protecting cells from overstimulation. These mechanisms involve activities of two families of proteins: i) G protein-coupled receptor kinases, serine-threonine kinases, capable of phosphorylation of receptor and thus uncoupling receptor-G protein, and ii) beta-arrestins with "scaffold" function of the G protein, transducing signal leading to activation of mitogen-associated protein (MAP) kinase cascade. MAP kinase *via* specific kinases regulates a number of intracellular events, including apoptotic signals (Avissar and Schreiber 2006).

In vitro studies contribute to the clarification of the molecular basis of antidepressant action involving G proteins as postreceptor components (Alt *et al*. 2001, Donati and Rasenick 2005). Cell cultures represent alternative bioassay models to animal experiments. C6 glioma established cell line of astrocyte origin is used in the studies exploring antidepressant effects (Mareš *et al*. 1991, Kovářů *et al*. 2001, Donati and Rasenick 2005). Acute antidepressant administration lasts 24 h, chronic 5-day administration to C6 glioma cell cultures is comparable with 3-week antidepressant treatment of rats (Chen and Rasenick 1995).

According to our results, acute fluoxetine effect evoked a decreased level of G $\alpha_{q/11}$ subunit in C6 glioma cells, whereas an increased G $\alpha_{q/11}$ level was observed after chronic exposure. Acute fluoxetine administration causing a reduced membrane G $\alpha_{q/11}$ amount was linked to subunit translocation into cytoplasm where it was determined

(Kovářů *et al*. 1997, 1998). Reduced membrane G $\alpha_{q/11}$ subunit levels caused a lower degree of phospholipase C signaling with a subsequent decreased substrate 1,4,5-inositoltriphosphate formation. Anti-depressants from different classes are able to induce G α subunit translocation into the cytoplasm (Donati and Rasenick 2005). Intracellular consequences of fluoxetine administration on C6 glioma cells were demonstrated by apoptotic events in contrast to ineffective imipramine or amitriptyline (Španová *et al*. 1997). MAP kinase activation participating in apoptotic signals was detected in fluoxetin-treated cultures of rat astrocytes (Mercier *et al*. 2004).

We also studied *in vitro* chronic effects of sertraline, citalopram (SSRIs) and mirtazapine (noradrenergic and serotonergic antidepressant) in comparison with tricyclic imipramine, amitriptyline or desipramine. Results show that G α subunit profiles are antidepressant-dependent and are not affected by TCA administration. The data available demonstrate antidepressant-induced cell signal transduction pathway modulation *via* both effector enzymes, adenylylcyclase (G αs) and phospholipase C (G α q/11) (Kovářů *et al*. 1998, 1999, 2001).

When citalopram effects on both rat C6 glioma cells after *in vitro* chronic treatment and rat brain *in vivo* were compared, similarities in Gα profiles were observed (Fig. 1). *In vivo* citalopram effects were comparable in the brain and the spleen, indicating a similar cell signaling response in functionally different systems (Fišerová *et al*. 1997, Kovářů *et al*. 2000, 2001, Fišerová *et al.* 2002).

Conclusions

Despite several decades of research, the exact neurobiological substrate of depression and mechanisms of antidepressant drug action are still unknown. There is a complex disturbance of homeostatic functions in depression, comprising immune, endocrine and central nervous systems, which are regulated and/or corrected by antidepressant treatment. As suggested by many authors, disturbances in cellular plasticity processes, neurogenesis and suppression of reparation processes are the crucial changes at the cellular level in depression (Jacobs *et al.* 2000, Nestler *et al*. 2002, Kempermann and Kronenberg 2003, Duman 2004, Leonard 2006). Impairment of neural connectivity results in the aberrant information processing in neural circuits critical for mood regulation.

Depression is often accompanied by inflammatory changes and hypercortisolemia which are

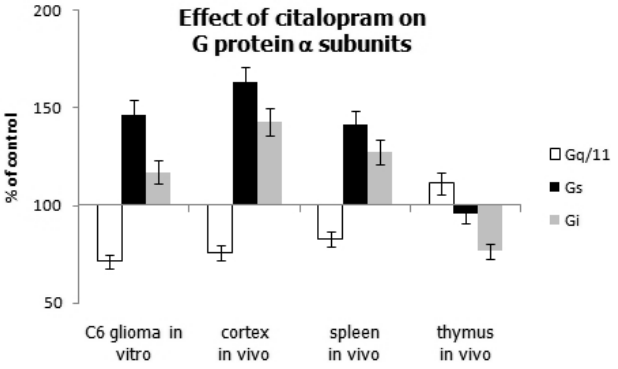

Fig. 1. Effect of citalopram *in vitro* and *in vivo* in the rat. Each result is the mean ± S.E.M. of 7-9 measurements. For details see Kovářů *et al.* (2001).

both pro-apoptotic. Many findings demonstrate an increase of apoptotic processes and atrophic changes in the hippocampus and frontal lobes as well as other structural neuronal alterations (Hayley *et al*. 2005, Shiepers *et al*. 2005, Lucassen *et al*. 2006).

Nevertheless, the present prevailing opinion considering only neuronal population as a substrate of a disorder and the only target of antidepressant medication is not further sustainable with a expanding knowledge demonstrating close functional cooperation between neurons and supportive glia in health and disease. This close cooperation is also reflected in the depression pathogenesis where degeneration of neuronal populations in certain regions is also accompanied by glial astheny and impairment of neuronal metabolism which is largely glia-dependent.

As we try to demonstrate, antidepressants affect glial cell signal transduction, as evidenced by changed G protein levels and second messenger changes. Treatment also modulates complex cell responses and production of many substances, necessary for neuronal health and survival, including a wide array of growth factors. The antidepressant treatment effect, which in some aspects opposes the effect of stress on neurons, is therefore not limited to neuronal population. Antidepressants also affect astrocytes, which are the major source of the neurotrophic and neuroprotective substances, thus supporting neuroplasticity events. Therefore, modulation of astrocyte activity seems to be a logical step in complex pharmacological treatment of depression as well as of other neuropsychiatric disorders with a neurodegenerative component. Considering significant differences in the antidepressant effects on astrocyte cell signal transduction, it remains a matter of further research to identify drugs with specific

modulatory effects on astrocytic function or production of neurotrophic molecules.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

Supported by grants: GA ČR 524/05/0267, MSM 0021620849 and IAA 500 2006 20.

Abbreviations

cAMP – cyclic adenosine monophosphate, CNS – central nerve system, EAA – excitatory amino acid, EGF – epidermal growth factor**,** GFAP – glial fibrillar acidic protein, IL – interleukin, NMDA – N-methyl D-aspartate, SSRI – selective serotonin reuptake inhibitor, TCA – tricyclic antidepressant, TNF – tumor necrosis factor.

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