Cell signalling in CNS and immune system in depression and during antidepressant treatment: focus on glial and natural killer cells

Hana Kovaru [1], Marek Pav [1], Frantisek Kovaru [2,3], Jiri Raboch [1], Anna Fiserova [4]

1. Charles University in Prague, 1st Faculty of Medicine, Prague, Czech Republic
2. University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic
3. Institute of Animal Physiology and Genetics, Academy of Sciences CR, Brno, Czech Republic
4. Institute of Microbiology, Academy of Sciences CR, Prague, Czech Republic

Correspondence to: Prof. RNDr. Hana Kovářů, DrSc.
Charles University in Prague, 1st Faculty of Medicine
120 00 Prague 2, Czech Republic
PHONE: +420 224965382, FAX: +420 224923077,
E-MAIL: hkova@lf1.cuni.cz

Submitted: 2009-05-04 Accepted: 2009-08-17 Published online: 2009-09-15

Key words: **astrocyte; cAMP; depression; antidepressant; glia; GTP binding protein; natural killer (NK)**

Neuroendocrinol Lett 2009; **30**(4):421–428 **PMID:** 20010506 NEL300409A16

Abstract

CNS, endocrine and immune systems share the same molecules: neurotransmitters, cytokines and hormones to communicate within and among each other. Depression is associated with abnormalities in the noradrenergic, serotonergic and dopaminergic neurotransmitter systems and reductions in the level of their precursors and metabolic turnover. Most of these signalling molecules use trimeric G-proteins as a transduction system to transfer extracellular signal into cellular response. Altered levels or function of signalling proteins, especially α subunits of trimeric G-proteins, were found in post-mortem brain tissue and leukocytes of subject suffering from major depression.

There is a considerable evidence that inflammatory response and immune system changes are the part of depression. Components of cellular immune system natural killer cells, important effectors of immune surveillance, are sensitive to stress response, and their functions are compromised in depressive subjects. Many lines of evidence also point to the loss of both neuronal and glial plasticity and neurotrophic factor support under chronic stress or in depression. There is an increasing knowledge of the role of astrocytic cells in neuroplastic processes and neurotransmitter metabolism. Alterations in the glial populations are observed in major depressive subjects. Antidepressant treatment is modulating glial signalization cascades, increasing production of neurotrophic molecules, supporting neuroplasticity processes, and also modulating functions of natural killers. At the level of membrane signalling, antidepressants show a direct influence upon Gα subunit levels in both immune system and CNS. These findings support the view that antidepressants influence activity of natural killer and astrocytic populations, and this could be of importance in the depression etiopathogenesis and/or treatment.

REVIEW

Abbreviations:

ACTH – adrenocorticotropic hormone
ATP – adenosine triphosphate
AC – adenylyl cyclase
cAMP – cyclic adenosine monophosphate
BDNF – brain derived neurotrophic factor
CREB – cAMP response element binding protein
CNS – central nervous system
DAC – diacylglycerol
G-protein – trimeric GTP binding protein
FGF – fibroblast growth factor
GDNF – glia derived neurotrophic factor
GTP – guanosine triphosphate
IL-1β – interleukine 1- β
IL-6 – interleukine 6
IL-10 – interleukine 10
INF-γ – interferon γ
$InsP_3$, IP3 – 1,4,5 inositol triphosphate
MAOA – monoamine oxidase A
NA – noradrenaline
NGF – nerve growth factor
NK – natural killer
NKCA – natural killer cytotoxic activity
5-HT – 5-hydroxytryptamine, serotonin
PKA – protein kinase A
PLC – phospholipase C
PKC – protein kinase C
SSRI – selective serotonin reuptake inhibitor
S100- β – trophic factor S100β
TCA – tricyclic antidepressant
TGF-β – transforming growth factor β
TNF- α – tumor necrosis factor α

Introduction

There is a widening knowledge of complex interactions among the main homeostatic systems: nervous, immune and endocrine in health and under pathological conditions. One of disorders where a complex disturbance of all systems is present, is major depression. Depression is a highly prevalent disorder, affecting 10–20% of population, with a higher prevalence in women (Weissman *et al.* 1996). Its prominent symptoms are depressive mood, anhedonia, loss of self-confidence, and suicidal ideation. There are also problems with concentration, decision making, and other signs of cognitive impairment. Depressive people often present somatic complaints such as pain, insomnia, loss of appetite, and decrease of body weight (Sadock and Sadock 2005). Neuroendocrine dysfunction of HPA axis is part of major depression symptoms (Matalka, 2003). There are also endocrine abnormalities in depressive patients, 50% of depressive patients have elevated levels of urine cortisol, and administration of synthetic corticoid dexamethazone does not result in suppression of cortisol blood levels and ACTH secretion (Mendlewicz *et al.* 1984; Watson *et al.* 2006). These patients are at a higher risk of suicidium (Joniken *et al.* 2007). Elevated cortisol levels are implicated in the impairment of neuroplastic processes and diminished availability of growth factors like BDNF, NGF or FGF (Duman *et al.* 1997; Evans *et al.* 2004; Hayley *et al.* 2005).

The CNS, endocrine and immune systems use neurotransmitters, cytokines and hormones to cross-talk communication among them (Haddad *et al.* 2002; Kitzlerová and Anders 2007; Anismann *et al.* 2008). Most of this signalling molecules use G-proteins for transduction of extracellular signal into cellular response. After ligand binding to G-protein coupled receptor, the trimeric protein complex α,β,γ G-protein subunits is dissociating, activated α subunit of G-protein is then initiating cascade of intracellular events: protein phosphorylations, ion channel modulation and activation of further signalization components (Wettschureck and Offermanns 2005; Avissar and Scheiber 2006; Luttrell 2006). Mode of pathway activation is dependent on the α subunit type (Wettschureck and Offermanns 2005). Gαs subunits activate adenylyl cyclase (Gαi inhibits enzyme). Gαs increase cAMP formation, activation of protein kinase A, phosphorylation of transcription CREB factor. The Gαq subunit is initiating PLC cascade activation, increase of inositol 1,4,5-triphosphate ($InsP_3$) production and release of Ca^{2+} from intracellular stores, production of diacylglycerol and protein kinase C (PKC) activation (Hubbard and Hepler 2006).

Although antidepressant medication has been used to treat affective disorders for more than 50 years, our understanding of its action is still incomplete. Acute action is thought to be mediated by blockade of serotonin (5-HT) or noradrenaline (NA) reuptake, chronic administration results in modulation of the cellular signalling components via increased levels of serotonin, noradrenaline and dopamine acting on specific receptors (Duman *et al.* 1997; Nestler *et al.* 2002; Normann *et al.* 2007, Dronjak et al.2007). Antidepressants are known to modulate density of neurotransmitter β-adrenergic receptors when administered chronically (Honegger *et al.* 1986; Fishman and Finberg 1987). Nevertheless, in contrast to tricyclic antidepressants, down-regulation of β-adrenoreceptor density by SSRIs has not been consistently demonstrated (Nelson *et al.* 1990; Koe and Lebel 1995). Clinically effective antidepressants facilitate G-protein activation of adenylyl cyclase without altering G-protein content (Menkes *et al.* 1983; Chen and Rasenick 1995).

Chronic antidepressant effect on C6 glioma cells prevents Gαs subunit accumulation in cytoskeletal associated plasma membrane domains, causing its redistribution to the cytoplasm, which can partially explain reduced Gαs subunit coupling as well as elevated Gαs subunit – adenylyl cyclase coupling (Donati and Rasenick 2005). Because this effect occurs also in *in vitro* cultures which lack presynaptic input, this can be also considered a direct postsynaptic action of antidepressants on signalling components (Chen and Rasenick 1995).

Several lines of evidence suggest that long-term antidepressant treatment is facilitating signalization cascade initiated by Gαs subunit, with subsequent activation of adenylyl cyclase, increased cAMP formation, facilitation of transcription mediated by CREB (cAMP response element binding protein) and enhanced production of neurotrophins in the CNS, including BDNF (Chen and Rasenick 1995; Nestler *et al.* 2002; Nair and

Vaidya; 2006; Norman *et al.* 2007). Resulting changes of cell viability, neuroplastic changes and increased neurogenesis, especially in the hippocampal region, are considered to mediate at least a part of the antidepressant effect (Duman *et al.* 1997; Nestler *et al.* 2002; Duman and Monteggia 2006).

Immune changes and depression

It has been suggested that immune activation and increased levels of inflammatory cytokines (IL-1,TNF- α, INF-γ) with subsequent behavioral (so-called sickness behavior) and biological changes (HPA axis activation) is a characteristic of depression (Leonard 2001; Haddad *et al.* 2002; Simpkins and Devine 2003; Simon *et al.* 2007; Maes 2008). In the CNS environment, inflammatory cytokines like IL-1β are identified as one of neurotoxic mediators, suppressing hippocampal progenitor cell proliferation and mediating effect of chronic stress; blockade of IL-1β receptors alleviates chronic stress effect (Koo and Duman 2008). There is also widely recognised complex relationship between chronic stress, depression and immune functions, leukocytes are sensitive to stress-induced systemic cortisol or monoamine levels, monoamine receptors are widely expressed on leukocytes, including α- a β-adrenoreceptors and dopamine receptors (Haddad *et al.* 2002; Fišerová *et al.* 2002; Kovářů and Kovářů 2005).

One of the most consistently demonstrated immune changes in depressive subjects is decreased natural killer cytotoxic activity (NKCA) (Reynaert *et al.* 1995; Zorrilla *et al.* 2001). Natural killer (NK) cells are released to circulation in response to stressor stimuli, form the important elements of innate immune defence against viral infections and malignant tumor growth (Engler *et al.* 2004; Orange and Ballas 2006). NK cells are capable of early cytokine production and induce lysis of target cells without prior antigen sensitisation (Cooper *et al.* 2001). There is an association between inflammatory cytokine levels (TNF-α, IL-6) and diminished NKCA in the depressive senior population (Trzonkowski *et al.* 2004). Activity of NK cells is regulated directly by hypothalamic nuclei and by a wide array of receptors, including those for catecholamines; resulting level of activity is a consequence of complex signalization response of activation and inhibitory signals (Katafuchi *et al.* 1993; Jetschmann *et al.* 1997; Kirwan and Burshtyn 2007). Impaired NKCA was repeatedly demonstrated in major depressive subjects with restoration of activity following antidepressant treatment concurrently with amelioration of depressive symptoms (Frank *et al.* 1999; Zorrilla *et al.* 2001; Evans *et al.* 2007). There is a significant association between depressive symptoms, NK numbers and NKCA, and survival time in patients with malignity (Steel *et al.* 2007).

There is also consistent demonstration of serotonin stimulated cAMP formation in leukocytes of major depressive disorder subjects (Halper *et al.* 1988; Mann *et al.* 1997; Gurguis *et al.* 1999). Analyses of peripheral blood granulocytes or thrombocytes of depressive patients confirmed relationship between alteration in G-proteins and decreased isoprotenol or β-adrenoreceptor induced cAMP accumulation in subjects suffering from major depression (Halper *et al.* 1988; Gurguis *et al.* 1999). Furthermore, an association between G-protein β3 subunit gene polymorphism and severity of depression symptoms and response to antidepressant treatment was demonstrated (Lee *et al.* 2004).

Antidepressants and leukocytes

Chronic antidepressant treatment alleviates macrophage-produced cytokine production and blocks its behavioral consequences, and also restores NK activity (Kubera *et al.* 1995; Frank *et al.* 1999; Maes, 2001; Evans *et al.* 2007). Increases in potentiation of β_2-adrenoreceptor- mediated cAMP responses in leukocytes of depressed subjects were found during antidepressant or electroconvulsive therapy, and were correlated with improvement of depression (Mann *et al.* 1990; Halper *et al.* 1988). We previously demonstrated dynamic changes in levels of both Gα q/11 and Gαs subunits of peripheral blood granulocytes of patients with depression during fluoxetine administration on days 3 – 28 (Kovářů *et al.* 1997; 2000; Kovářů and Kovářů 2005). Analyses of peripheral blood granulocytes or thrombocytes of depressive patients show relationship between alteration in G-proteins and decreased Gα-subunit function in depression; granulocyte Gα-subunit levels were suggested as a depression „state marker" or a predictor of antidepressant therapeutic response (Gurguis *et al.* 1999; Avissar and Schreiber 2006). In the depression pathophysiology, regulators of G-protein signalling are also involved, several results show reduced β-arrestin1 and GRK2 kinase levels in leukocytes of subjects suffering from major depression with normalization of levels following antidepressant treatment (Matuzany-Ruban *et al.* 2005; Avissar and Schreiber 2006).Our data demonstrate modulation of Gα subunit levels in human- and rat NK cell culture by amitriptyline and fluoxetine by the same primary antibodies. Antibody properties to detect of Gα chain in both human and rat cell culture are based on common primary amino acid sequences of C terminal dekapeptides of alpha subunits of main types of G proteins in mammals (Milligan 1988; Kovářů *et al.* 2001; Kovářů and Kovářů 2005).

There is a decrease of NKCA after acute fluoxetine administration in rats which is transient and followed by tolerance to chronic fluoxetine administration (Pellegrino and Bayer 1998). This effect is attributed to desensitisation of serotonergic receptors involved in the immunoregulatory pathway regulating NK activity (Artigas *et al.* 1996; Pellegrino and Bayer 1998). An increase of NK activity was found after 5-day treatment

with amitriptyline *in vivo* (Kubera *et al.* 1995). Augmentation of NKCA activity after chronic fluoxetine administration *in vivo* and also *in vitro* is repeatedly demonstrated (Frank *et al.* 1999; 2004).

Our finding shows direct modulation of NK signalization by antidepressants which is not dependent on central influence; more prominent changes are induced by fluoxetine than by amitriptyline (Kovářů *et al.* 1997). Reduced levels of Gαq/11 subunits in both human and rat NK cell line could impair functioning of PLC pathway, both DAG and $InsP_3$ stimulate PKC activity and all enzymes participate in the release of cytotoxic granules and lysis of tumor target cells by NK (Steele an Brahmi 1988; Procopio *et al.* 1989). NK cytotoxic activity is regulated also by the adenylyl cyclase system, elevation of cAMP is associated with suppression of NKCA, and this inhibition appears dependent on PKA activation (Whalen and Bankhurst, 1990; Torgersen *et al.* 1997). However, a further finding by Bariagaber and Whalen demonstrates that also inhibition of cAMP pathway results in suppression of NKCA, maintaining capacity to activate cAMP signalling pathway seems to be crucial for preserving NKCA (Bariagaber and Whalen 2003). Beside this, PLC pathway activation which is critical in the cytotoxic response in the NK cells, is also dependent on the cAMP levels and PKA activation (Bariagaber and Whalen 2003).

Glia and depression

An increasing knowledge indicate the role of glial, especially astrocytic cells in the neuronal metabolic support, neurotransmitter metabolism, and synaptic regulation (Araque *et al.* 1999; Haber and Murray 2006; Perea and Araque 2005a;2005b). Furthermore, astrocytes are implicated in active participating in the induction of new synapses, synaptic communication, and influence experience-dependent changes in the synaptic strength (Elmariah *et al.* 2005; Kleim *et al.* 2007). There is an evidence demonstrating unanticipated reductions in the density and number of glial cells in the regions of importance in subject suffering from major depression, including the dorsolateral and frontoorbital cortex and possibly the limbic structures (Rajkowska *et al.* 1999; Rajkowska and Miguel-Hidalgo 2007). These observations led to the hypothesis that glial cell dysfunction may contribute to the pathogenesis of depression and antidepressant action (Coyle and Schwarcz 2000; Cotter at al. 2001; Manev *et al.* 2003; Páv *et al.* 2008).

A recent finding demonstrates that selective pharmacological glial ablation in the prefrontal cortex of experimental animals is able to induce behavior similar to chronic stress-induced behavior and supports thus the hypothesis that glial population losses contribute to development of core depression symptoms (Banasr and Duman 2008). There are also findings suggesting that astrocyte structural and functional heterogeneity can be of importance in the depression neuropathology (Won and Oh 2000; Rajkowska and Miguel-Hidalgo 2007).

Astrocytic cells are able to respond to changes in the CNS environment such as trauma, inflammation, infection or neuronal damage; rearrange the profile of expressed receptors and secreted molecules, and adopt "reactive" phenotype (Ridet *et al.* 1997). Astrocytes respond to cytokines like IL-1, IL-6, INF-γ or TNF-α, ATP, adenosine, growth factors like FGF2 or peptide hormones like vasopressin (Sofroniew 2005).

Astrocytes are able to produce growth factors as GDNF, NGF, BDNF, neuropoietic and anti-inflammatory cytokines like IL-4, IL-10 and RANTES chemokine (Althaus and Richter-Landsberg 2000; Miklic *et al.* 2004; Juric *et al.* 2006). Glucocorticoids regulate astrocyte growth factor production (S100-β, TGF-β, NGF or BDNF), this is dependent on the dynamics of corticoid levels (Niu *et al.* 1997; Gubba *et al.* 2004). Secerned molecules as immune system mediators signal between astrocytes, neurones, microglia and endothelial cells (Farina *et al.* 2007). Astrocytes by anti-inflammatory cytokine IL-4, IL-10 and IL-13 secretion limit inflammatory activation as well as activation of microglia (Ledeboer *et al.* 2000).

Astrocyte-microglia interaction is also important in the serotonin metabolism; activated microglia is producing toxic metabolites like quinolinic acid from serotonin precursor tryptophan (Guillemin *et al.* 2001). Inflammation and elevated levels of inflammatory cytokines induce increasing activity of indoleamine (2,3)-dioxygenase, thus decreasing levels of tryptophan and serotonin production, and increasing production of toxic metabolites which have apoptotic, pro-oxidant and neurotoxic effects and aggravate initial inflammation (Maes *et al.* 2007). Astrocytes are able to metabolise these toxic metabolites and produce neuroprotective kynurenine acid with antiapoptotic and neuroprotective effects, and limit the inflammatory processes and neuronal damage (Guillemin *et al.* 2001).

Antidepressants and glial cells

Antidepressant effects are usually studied on brain tissue, neuronal cells or neuronal cell models and results are interpreted in terms of neuronal function modulation, with some exceptions – astrocytes are not usually considered as a target of antidepressant action (Hertz and Richardson 1983; Cotter *et al.* 2001; Manev *et al.* 2003; Hertz *et al.* 2004; Lee *et al.* 2007). These cells, however, have been shown to respond to antidepressants in a manner similar to postsynaptic neurons and are used to study antidepressant effects (Chen and Rasenick 1995; Chung *et al.* 2007; Hisaoka *et al.* 2001; 2007). Astrocytes produce various neurotrophins – GDNF, BDNF, NGF and S100beta as an effect of antidepressant treatment, and antidepressant are able to reverse unfavourable effects of chronic

stress and depression (Condorelli *et al.* 1994; Manev *et al.* 2001; Hisaoka *et al.* 2001; Juric el al. 2006; Hisaoka *et al.* 2007).

Glial cells express β-adrenergic and 5-HT1A receptors in the high density and are considered by some authors as major target of neuronally released noradrenaline or serotonin *in vivo* (Feinstein *et al.* 2002; Hertz *et al.* 2004). Noradrenergic effects on astrocytes are essential for memory processes, synthesis of glutamate, morphological plasticity, membrane transport and immunological responses, and play role in the pathogeneses of several CNS diseases, including mood disorders (Hertz *et al.* 2004; Gavrilyuk *et al.* 2005). Moreover, monoaminergic neural activity regulates BDNF synthesis in the cultured rat astrocytes (Juric *et al.* 2006).

Stimulation of receptors positively coupled to adenylyl cyclase (e.g. β-adrenergic), increased Gαs subunit levels, or otherwise elevated cAMP levels exert profound influence upon glial functions. Cyclic AMP is inducing stellation of *in vitro* astrocyte growth which adopt a similar to their *in vivo* appearance through the depolymerisation of actomyosin stress fibres, reorganization of membrane compounds and does not require PKA activation (Goldman and Abramson 1990; Baorto *et al.* 1992; Won and Oh 2000). Change of cAMP levels also influence cellular responsiveness to other signalling events. Increased astrocyte cAMP levels enhance expression of glutamate GLAST transporters and glutamate uptake; this can affect participation of astrocytes in plastic processes and even transfer and storage of synaptic information (Perea and Araque 2005).

Number of data also demonstrate an interaction of cyclic AMP and $InsP_3$ system in cultured astroglial cells, both adenylyl cyclase and PLC, participating in the downstream signalling responsible for the stimulation of BDNF synthesis via CREB phosphorylation with previous activation of CaM kinase and MAP kinase cascades (Hannson *et al.* 1990; Miklic *et al.* 2004; Tiraboshi *et al.* 2004). Elevation of cAMP levels has a suppressive effect on astrocytic expression of genes involved in inflammation which can participate in the suppression of inflammatory mechanisms, suggested in the depression etiopathogenesis such as IL-1, TNF-α, NO synthase or adhesion molecule production (Feinstein *et al.* 2002; Hayley *et al.* 2005; Gavrilyuk et al.2005). Neuroprotection can be also increased (Junker *et al.* 2002; Mourlevat *et al.* 2003).

Some findings suggesting significantly elevated Gαq/11 levels and stimulation of PLC pathway in astrocyte cells as an effect of chronic administration of antidepressant drugs with different modes of action such as fluoxetine, mianserine and imipramine (Lesch *et al.* 1992b; Fakuda *et al.* 1994). Acute fluoxetine administration causing reduced membrane associated Gαq/11 subunit amount was analyzed and translocation into cytoplasm was determined (Kovářů *et al.* 1997).

There is astrocyte growth factor production including BDNF and GDNF after activation of Ca^{2+} -dependent kinases cascades, protein kinase C (PKC) cascades and MAP kinases signalling pathway activation (Miklic *et al.* 2004; Mercier *et al.* 2004; Saito *et al.* 2006; Hisaoka *et al.* 2007). Cultured astrocytes express sodium-dependent serotonin transporters (SERT); phosphorylation of SERT by PKC or translocation of PKC from cytoplasm to membrane is reducing serotonin uptake (Kimelberg and Katz 1985; Inazu *et al.* 2001). There is also an involvement of PKC in β-adrenoreceptor down-regulation, inhibition of protein kinase C attenuated both isoproterenol-induced and desipramine induced β-adrenoreceptor down-regulation in glioma cells and results in a more prolonged repression of receptor gene transcription (Li *et al.* 1998; Leavitt *et al.* 2001).

Increases of glial Ca^{2+} concentrations can spread to neighbouring astrocytes through gap junctions as "Ca^{2+} wave" and stimulate responsivity of astroglial syncytium and release of gliotransmitters such as glutamate or D-cycloserine (Araque *et al.* 1999; Parpura and Haydon 2000; Perea and Araque 2005a; 2005b; 2007). There are several lines of evidence suggesting excitatory amino acid neurotransmitter system in the pathophysiology and treatment of mood disorders (Krystal *et al.* 2002; Paul and Skolnick 2003; Müller and Schwartz 2007). Acting on NMDA receptors, astrocyte-derived glutamate can modulate excitability of neighbouring neurones, modulate processes of long-term plasticity and have influence upon neuronal firing synchronization, so astrocytes can even be considered as cellular elements involved in the information processing (Perea and Araque 2005a; 2005b; 2007). This, together with possible impairment of glutamine-glutamate cycle between astrocytes and neurones in certain areas (e.g. amygdala, hippocampus), can contribute to behavioral and physiological endophenotypes related to mood disorders (Lee *et al.* 2007).

Conclusion

Findings discussed above implicate modulation of glial cells G alpha subunits levels and subsequent signalization cascades modulation in the chronic effects of antidepressants. In contrast to tricyclic antidepressants which do not significantly influence G-protein subunits levels, newer molecules modulate Gαq/11 subunits in a much larger extent. Substantial amount of data also support the view that antidepressants influence activity and cellular production of leukocytes, and this can be of importance in the depression etiopathogenesis and/or treatment, or can be used as a measure of treatment outcome. Direct effects of antidepressants upon natural killer signalization cascades influence production of cytokines and directly modulate cytotoxic effector activity. Modulation of natural killer functions can thus have an impact on the chronic infection course, cytokine production during

stress response or influence tumor growth. Comparison of profiles of Gα subunit changes following antidepressant administration in vivo using rat model – in brain and spleen or in vitro in C6 glioma (astrocytoma) and NK cells could suggest a similar antidepressant-induced cell signalling in different functional systems, and presumable influencing by antidepressant treatment. Further research is needed to detailed knowledge of antidepressant influence at the organ level – CNS and immune system or at the cellular level – glial- and/or NK cells in the neuroendocrine-immune relationship and pathophysiology of depressive disorder.

Acknowledgements. This study was supported by grant of Academy of Sciences of Czech Republic, No. IAA 601680801 and grants of Ministery of Education of Czech Republic, No.MSM 0021620849 and No. 6215712403.

REFERENCES

1 Althaus HH, Richter-Landsberg C (2000). Glial cells as targets and producers of neurotrophins. Int Rev Cytol. **197**: 203–277.
2 Anisman H, Merali Z, Hayley S (2008). Neurotransmitter, peptide and cytokine processes in relation to depressive disorder: Comorbidity between depression and neurodegenerative disorders. Prog Neurobiol. **85**(1): 1–74.
3 Araque A, Parpura V, Sanzgiri RP, Haydon PG (1999). Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci. **22**: 208–215.
4 Artigas FL, Romero De Montigny C, Blier P (1996). Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT_{1A} antagonists. Trends Neurosci. **19**: 378–383.
5 Avissar S, Schreiber G (2006). The involvement of G proteins and regulators of receptor-G protein coupling in the pathophysiology, diagnosis and treatment of mood disorders. Clin Chim Acta. **366**: 37–47.
6 Banasr M, Duman R (2008). Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviours. Biol Psychiatry. **64**(10): 863–870.
7 Baorto DM, Mellado W, Shelanski ML (1992). Astrocyte process growth induction by actin breakdown. J Cell Biol. **117**: 357–367.
8 Bariagaber AK, Whalen MM (2003). Decreased adenylyl cyclase and cAMP-dependent protein kinase activities inhibit cytotoxic function of human natural killer cells. Hum Immunol. **64**: 866–873.
9 Chen J, Rasenick MM (1995). Chronic treatment of C6 glioma cells with antidepressant drugs increases functional coupling between a G protein (Gs) and adenylyl cyclase. J Neurochem. **64**: 724–732.
10 Chung EY, Shin SY, Lee YH (2007). Amitriptyline induces early growth response -1 gene expression via ERK and JNK mitogen-activated protein kinase pathways in rat C6 glial cells. Neurosci Lett. **422**: 43–48.
11 Condorelli DF, Dell'Albani P, Mudò G, Timmusk M, Belluardo N (1994). Expression of neurotrophins and their receptors in primary astroglial cultures: induction by cyclic AMP-elevating agents. J Neurochem. **63**: 509–516.
12 Cooper MA, Fehniger TA, Caligiury MA (2001). The biology of human natural killer-cell subsets. Trends Immunol. **22**: 633-640.
13 Cotter DR, Pariante CM, Everall IP (2001). Glial cell abnormalities in major psychiatric disorders: the evidence and implications. Brain Res Bull. **55**: 585–595.
14 Coyle JT, Schwarcz R (2000). Mind glue: implications of glial cell biology for psychiatry. Arch Gen Psychiatry. **57**: 90–93.
15 Donati RJ, Rasenick MM (2005). Chronic antidepressant treatment prevents accumulation of Gs alpha in cholesterol-rich, cytoskeletal-associated, plasma membrane domains (lipid rafts). Neuropsychopharmacology. **30**: 1238–1245.
16 Dronjak S, Spasosjevic N, Gavrilovic L, VaragicV (2007). Effect of noradrenaline and serotonin reuptake inhibitors on pituitary-adrenocortical and sympatho-adrenomedullar system of adult rats. Neuroendocrinol Lett **28 :** 614–620.
17 Duman RS, Heninger GR, Nestler EJ (1997). A molecular and cellular theory of depression. Arch Gen Psychiatry. **54**: 597–606.
18 Duman RS, Monteggia LM (2006). A neurotrophic model for stress-related mood disorders. Biol Psychiatry. **59**(12): 1116–1127.
19 Elmariah SB, Hughes EG, Oh EJ, Balice-Gordon RJ (2005). Neurotrophin signalling among neurons and glia during formation of tripartite synapses. Neuron Glia Biol. **1**: 1–11.
20 Engler H, Dawils L, Hoves S, Kurth S, Stevenson JR, Schauenstein K, Stefanski V (2004). Effects of social stress on blood leukocyte distribution: the role of α- and β-adrenergic mechanisms. J Neuroimmunol. **156**: 153–162.
21 Evans S, Choudary CR, Neal JZ, Li MP, Vawter H, Tomita H, Lopez JF, Thomson RC, Meng F, Stead JD, Walsh SM, Myers RM, Bunney WE, Watson SJ, Jones EG, Akil H (2004). Dysregulation of the fibroblast growth factor system in major depression. Proc Natl Acad Sci USA. **101**: 15506–15511.
22 Evans DL, Lynch KG, Benton T, Dubé B, Gettes DR, Tustin NB, Lai JP, Metzger D, Douglas SD (2007). Selective serotonin reuptake inhibitor and substance P antagonist enhancement of natural killer innate immunity in human immunodeficiency virus/acquired immunodeficiency syndrome. Biol Psychiatry. **63**(9): 899–905.
23 Farina C, Aloisi F, Meinl E (2007). Astrocytes are active players in cerebral innate immunity. Trends Immunol. **28**(3): 138–145.
24 Fakuda H, Nishida A, Saito H, Shimizu M, Yamawaki S (1994). Imipramine stimulates phospholipase C activity in rat brain. Neurochem Int. **25**: 567–571.
25 Feinstein DL, Heneka MT, Gavrilyuk V, Dello Russo C, Wienberg G, Galea E (2002). Noradrenergic regulation of inflammatory gene expression in brain. Neurochem Int. **41**: 357–365.
26 Fišerová A, Starec M, Kuldová M, Kovářů H, Páv M, Vantucci L, Pospíšil M (2002). Effects of D2-dopamine and alpha-adrenoreceptor antagonists in stress induced changes on immune responsiveness of mice. J Neuroimmunol. **130:** 55–65.
27 Fishman PH, Finberg JP (1987). Effect of the tricyclic antidepressant desipramine on beta-adrenergic receptors in cultured rat glioma C6 cells. J Neurochem. **49**: 282–289.
28 Frank MG, Hendricks SE, Johnson DR, Wieseler JL, Burke WJ (1999). Antidepressants augment natural killer cell activity: in vivo and in vitro. Neuropsychobiology. **39**: 18–24.
29 Frank MG, Hendricks SE, Burke WJ, Johnson DR (2004). Clinical response augments NK cell activity independent of treatment modality: a randomized double-blind placebo controlled antidepressant trial. Psychol Med. **34**: 491–498.
30 Gavrilyuk V, Kalinin S, Hilbush BS, Middlecamp A, McGuire S, Pelligrino D, Weinberg G, Feinstein DL (2005). Identification of complement 5a-like receptor (C5L2) from astrocytes: characterization of anti-inflammatory properties. J Neurochem. **92**: 1140–1149.
31 Goldman JE, Abramson B (1990). Cyclic AMP-induced shape changes of astrocytes are accompanied by rapid depolymerisation of actin. Brain Res. 528: 189–196.
32 Gubba EM, Fawcett JW, Herbert J (2004). The effects of corticosterone and dehydroepiandrosterone on neurotrophic factor mRNA expression in primary hippocampal and astrocyte cultures. Brain Res Mol Brain Res. **127**(1–2): 48–59.
33 Guillemin GJ, Kerr SJ, Smythe GA, Smith DG, Kapoor V, Armati PJ, Croitoru J, Brew, BJ (2001). Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection. J Neurochem. **78**(4): 842–853.
34 Gurguis GN, Vo SP, Griffith JM, Rush AJ (1999). Neutrophil beta(2)-adrenoceptor function in major depression: G(s) coupling, effects of imipramine and relationship to treatment outcome. Eur J Pharmacol. **386**: 135–144.
35 Haber M, Murray KK (2006). Reshaping neuron-glial communication at hippocampal synapses. In: Neuron Glia Biology 2, Cambridge University Press, pp. 59–66.
36 Haddad JJ, Saadé NE, Safieh-Garabedian B (2002). Cytokines and neuro-immune-endocrine interactions: a role for the

hypothalamic-pituitary-adrenal revolving axis. J Neuroimmunol. **133**: 1–19.
37 Halper JP, Brown RP, Sweeny JA, Kocsis JH, Peters A, Mann JJ (1988). Blunted β-adrenergic responsivity of peripheral blood mononuclear cells in endogenous depression. Arch Gen Psychiatry 45: 241–244.
38 Hannson E, Simonsson P, Alling C (1990). Interactions between cyclic AMP and inositol phosphate transduction systems in astrocytes in primary culture. Neuropharmacology. 2: 591–598.
39 Hayley S, Poulter MO, Merali Z, Anisman H (2005). The pathogenesis of clinical depression: stressor- and cytokine-induced alterations of neuroplasticity. Neuroscience. **135**: 659–678.
40 Hertz L, Chen Y, Gibbs ME, Zang P, Peng L (2004). Astrocytic adrenoceptors: a major drug target in neurological and psychiatric disorders? Curr Drug Targets CNS Neurol Disord. **3**: 239–267.
41 Hisaoka K, Nishida A, Koda T, Miyata M, Zensho H, Morinobu S, Ohta M, Yamawaki S (2001). Antidepressant drug treatments induce glial cell line-derived neurotrophic factor (GDNF) synthesis and release in rat C6 glioblastoma cells. J Neurochem. 79: 25–34.
42 Hisaoka K, Takebayashi M, Tsuchioka M, Maeda N, Nakata Y, Yamawaki S (2007). Antidepressants increase glial cell line-derived neurotrophic factor production through monoamine independent activation of protein tyrosine kinase and extracellular signal-regulated kinase in glial cells. J Pharmacol Exp Ther. **321**: 148–157.
43 Honegger UE, Disler B, Wiesmann UN (1986). Chronic exposure of human cells in culture to the tricyclic antidepressant desipramine reduces the number of beta-adrenoceptors. Biochem Pharmacol. **35**: 1899– 1902.
44 Hubbard KB, Hepler JR (2006). Cell signalling diversity of the Gqα family of heterotrimeric G proteins. Cell Signal. **18**(2): 135–150.
45 Inazu M, Takeda H, Ikoshi H, Sugisawa M, Uchida Y, Matsumiya T (2001). Pharmacological characterization and visualization of the glial serotonin transporter. Neurochem Int. **39**: 39–49.
46 Jetschmann JU., Benschop R., Jacobs R, Kemper A, Oberbeck R, Schmidt RE, Schedlowski M (1997). Expression and in-vivo modulation of alpha- and beta-adrenoreceptors on human natural killer (CD16+) cells. J Neuroimmunol. 7**4:** 159–164.
47 Joniken J, Carlborg A, Mårtensson B, Forslund K, Nordström AL, Nordström P (2007). DST non-suppression predicts suicide after attempted suicide. Psychiatry Res. **150**(3): 297–303.
48 Junker V, Becker A, Hühne R, Zembatov M, Ravati A, Culmsee C, Krieglstein J (2002). Stimulation of beta-adrenoceptors activates astrocytes and provides neuroprotection. Eur J Neuropharmacol. **446**: 25–36.
49 Juric DM, Miklic S, Carman-Krzan M (2006). Monoaminergic neuronal activity up-regulates BDNF synthesis in cultured neonatal rat astrocytes. Brain Res. **1108**: 54–62.
50 Katafuchi T, Ichijo T, Hori T (1993). Hypothalamic modulation of splenic natural killer cell activity in rats. J Physiol. **471**: 209–221.
51 Kimelberg HK, Katz DM (1985). High-affinity uptake of serotonin into immunocytochemically identified astrocytes. Science **228**: 889–891.
52 Kleim JA, Markham JA, Vij K, Freese JL, Ballard DH, Greenough WT (2007). Motor learning induces astrocytic hypertrophy in the cerebellar cortex. Behav Brain Res. **178**: 244–249.
53 Kirwan SE, Burshtyn DN (2007). Regulation of natural killer cell activity. Curr Opin Immunol. **19**(1): 46–54.
54 Kitzlerová E, Anders M (2007). The role of some new factors in the pathophysiology of depression and cardiovascular disease: Overview of recent research. Neuro Endocrinol Lett. **28**(6): 832–840.
55 Koe BK, Lebel LA (1995). Effects of serotoninergic agents on down regulation of beta-adrenoceptors by the selective serotonin reuptake inhibitor sertraline. Arch Int Pharmacodyn Ther. 329: 231–244.
56 Koo JW, Duman RS (2008). IL-1beta is an essential mediator oft he antineurogenic and anhedonic effects of stress. Proc Natl Acad Sci USA. **105**(2): 751–756.
57 Kovářů H, Fišerová A, Lisá V, Španová A, Kovářů F, Velek J (1997). Fluoxetine induced changes in C6 glioma cells and NK lymphocytes. In: Biologické základy psychických poruch. (Eds. J.Sikora, Z.Fišar et al.), Galén Publ Co, Praha: pp. 108–112.
58 Kovářů H, Fišerová A, Kovářů F, Paclt I, Lisá V (2000). Antidepressant or immunomodulator induced regulation of cell signalling in brain and immune system. Eur. Neuropsychopharmacol. **10**, Suppl 3: 269–270.
59 Kovářů H, Fišerová A, Kovářů F, Pospíšil M, Lisá V (2001). Modulation of heterotrimeric GTP-binding proteins in immune system and brain. Czech J Anim Sci. **46**: 62–67.
60 Kovářů H, Kovářů F (2005). Basis of neuroimmunomodulation. In: Základy neuroimunomodulace , Galén, Praha: pp. 203–208.
61 Krystal JH, Sanacora G, Blumberg H, Anand A, Charney DS, Marek G, Epperson CN, Goddard A, Mason GF (2002). Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. Mol Psychiatry. **7**(Suppl 1): S71–S80.
62 Kubera M, Basta-Kaim A, Skowron-Cendrzak A, Mazur-Kolecka B, Roman A, Boryc, J (1995). Effect of repeated amitriptyline administration to mice on the T lymphocyte proliferative activity and natural killer cell cytotoxicity. Pol J Pharmacol. **47**: 321–326.
63 Leavitt M, Setola V, Fishman PH (2001). Protein kinase C-mediated down-regulation of beta(2)-adrenergic receptor and gene expression in rat C6 glioma cells. J Neurochem. **77**: 823–829.
64 Ledeboer A, Brevé JJ, Poole S, Tilders FJ, Van Dam AM (2000). Interleukine-10, interleukine-4, and transforming growth factor-beta differentially regulate lipopolysaccharide-induced production of pro-inflammatory cytokines and nitric oxide in co-cultures of rat astroglial and microglial cells. Glia **30**: 134–142.
65 Lee HJ, Cha JH, Ham BJ, Han CS, Kim YK, Lee SH, Ryu SH, Kang RH, Choi MJ, Lee MS (2004). Association between G-protein beta3 subunit gene polymorphism and the symptomatology and treatment responses of major depressive disorders. Pharmacogenomics. **4**: 29–33.
66 Lee Y, Gaskins D, Anand A, Shekkar A (2007). Glia mechanisms in mood regulation: a novel model of mood disorders. Psychopharmacology (Berl). **191**: 55–65.
67 Leonard BE (2001). The immune system, depression and the action of antidepressants. Prog Neuropsychopharmacol Biol Psychiatry. **25**: 767–780.
68 Lesch KP, Hough CJ, Aulakh CS, Wolozin BL, Tolliver TJ, Hill JL, AkioyoshiJ, Chuang DM, Murphy DL (1992). Fluoxetine modulates G protein alpha s, alpha q, and alpha 12 subunit mRNA expression in rat brain. Eur J Pharmacol. **277**: 233–237.
69 Li Z, Vaidya VA, Alvaro JD, Iredale PA, Hzu R, Hoffmann G, Fidzgerald L, Curran PK, Machida CA, Fishmann PH, Duman RS (1998). Protein kinase C mediated down-regulation of À1-adrenergic receptor gene expression in rat C6 glioma cells. Mol Pharmacol. **54**: 14–21.
70 Luttrell LM (2006). Transmembrane signalling by G protein-coupled receptors. Methods Mol Biol. **332**: 3–49.
71 Maes M (2001). The immunoregulatory effect of antidepressants. Hum Psychopharmacol. **16**: 95–103.
72 Maes M, Mihaylova I, Ruyter MD, Kubera M, Bosmans E (2007). The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression - and other conditions characterized by tryptophan depletion induced by inflammation. Neuroendocrinol Lett. **28**(6): 826–831.
73 Maes M (2008). The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. Neuroendocrinol Lett. **29**(3): 287–291.
74 Mann JJ, Mahler JC, Wilner PJ, Halper JP, Brown RP, Johnson KS, Kocsis JH, Chen J (1990). Normalisation of blunted lymphocyte β-adrenergic responsivity in melancholic inpatients by a course of electroconvulsive therapy. Arch Gen Psychiatry. 47: 461–464.
75 Mann JJ, Halper JP, Wilner PJ, Sweeny JA, Mieczkowski TA, Chen JS, Stokes PE, Brown RP (1997). Subsensitivity of adenylyl cyclase-coupled receptors on mononuclear leukocytes from drug-free inpatients with a major depressive episode. Biol Psychiatry. **42**: 859–870.

76 Manev R, Uz T, Manev H (2001). Fluoxetine increases the content of neurotrophic protein S100beta in the rat hippocampus. Eur J Pharmacol. **420**: 1–2.
77 Manev H, Uz T, Manev R (2003). Glia as a putative target for antidepressant treatments.J Affect Disord. **75**: 59–64.
78 Matalka KZ (2003). Neuroendocrine and cytokines-induced responses to minutes, hours and days of mental stress. Neuroendocrinol Lett. **24** : 283–292.
79 Matuzany-Ruban A, Avissar S, Schreiber G (2005). Dynamics of beta-arrestin1 protein and mRNA levels elevation by antidepressants in mononuclear leukocytes of patients with depression. J Affect Disord. **88**: 307–312.
80 Mendlewicz J, Hubain PP, Koumakis C (1984). Further investigation of the dexamethasone suppression test in affective illnesses: relationship to clinical diagnosis and therapeutic response. Neuropsychobiology. **12**(1): 23–26.
81 Menkes DB, Rasenick MM, Wheeler MA, Bitensky MW (1983). Guanosine triphosphate activation of brain adenylate cyclase: enhancement by long-term antidepressant treatment. Science **219**: 65–67.
82 Mercier G, Lennon AM, Renouf B, Dessouroux A, Ramaugé M, Courtin F, Pierre M (2004). MAP kinase activation by fluoxetine and its relation to gene expression in cultured rat astrocytes. J Mol Neurosci. **24**: 207–216.
83 Miklic S, Juric DM, Carman-Krzan M (2004). Differences in the regulation of BDNF and NGF synthesis in cultured neonatal rat astrocytes. Int J Dev Neurosci. **22**: 119–130.
84 Mourlevat S, Troadec JD, Ruberg M, Michel PP (2003). Prevention of dopaminergic neuronal death by cyclic AMP in mixed neuronal/glial mesencephalic cultures requires the repression of presumptive astrocytes. Mol Pharmacol. **64**: 578–586.
85 Müller N, Schwartz MJ (2007). The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Mol Psychiatry. **12**: 988–1000.
86 Nair A, Vaidya VA (2006). Cyclic AMP response element binding protein and brain-derived neurotrophic factor: molecules that modulate our mood? J Biosci. **31**: 423–434.
87 Nelson DR, Palmer KJ, Johnson AM (1990). Effect of prolonged 5-hydroxytryptamine uptake inhibition by paroxetine on cortical beta 1- and beta 2-adrenoceptors in rat brain. Life Sci. **47**: 1683–1691.
88 Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002). Neurobiology of depression. Neuron. **34**: 13–25.
89 Niu H, Hinkle DA, Wise PM (1997). Dexamethasone regulates basic fibroblast growth factor, nerve growth factor and S100beta expression in cultured hippocampal astrocytes. Brain Res Mol Brain Res. **51**: 97–105.
90 Normann C, Schmitz D., Fűrmaier A, Doing C, Bach M (2007). Long-term plasticity of visually evoked potentials in humans is altered in major depression. Biol Psychiatry. **62**(5): 373–380.
91 Orange JS, Ballas ZK (2006). Natural killer cells in human health and disease. Clin Immunol.**118**(1): 1–10.
92 Páv M, Kovářů H, Fišerová A, Havrdová E, Lisá V. (2008) Neurobiological aspects of depressive disorder and antidepressant treatment: role of glia. Physiol Res. **57**(2): 151–164.
93 Parpura V, Haydon PG (2000). Physiological astrocytic calcium levels stimulate glutamate release to modulate adjacent neurons. Proc Natl Acad Sci USA. **97**: 8196–8234.
94 Paul IA, Skolnick P (2003). Glutamate and depression: clinical and preclinical studies. Ann N Y Acad Sci. **1003**: 250–272.
95 PellegrinoTC, Bayer BM (1998). Modulation of immune cell function following fluoxetine administration in rats. Pharmacol Bichem Behav. **59**: 151–157.
96 Perea G, Araque A (2005a). Properties of synaptically evoked astrocyte calcium signal reveal synaptic information processing by astrocytes. J Neurosci. **25**: 2192–2203.
97 Perea G, Araque A (2005b). Glial calcium signalling and neuron-glia communication. Cell Calcium. **38**: 375–382.
98 Perea G, Araque A. (2007) Astrocytes potentiate transmitter release at single hippocampal synapses. Science. **317**: 1083–1086.
99 Procopio AD, Paolini R, Gismondi A, Picolli M, Cavallo G, Frati L, Santoni A (1989). Effects of protein kinase C (PK-C) activators and inhibitors on human large granular lymphocytes (LGL): role of PK-C on natural killer (NK) activity. Cell Immunol. **118**: 470–481.
100 Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholzer JC, Roth BL, Stockmeier CA (1999). Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry. **45**: 1085–1098.
101 Rajkowska G, Miguel-Hidalgo JJ (2007). Gliogenesis and glial pathology in depression. CNS Neurol Disord Drug Targets. **6**: 219–233.
102 Reynaert , anne P, Body A, Staquet P., Zdanowicz N, Vause M, Chatelein B (1995): From health focus of control to immune control: internal locus has a buffering effect on natural killer cell activity decrease in major depression. Acta Psychiat Scand. **92**: 294–300.
103 Ridet JL, Malhotra SK, Privat A, Gage FH (1997). Reactive astrocytes: cellular and molecular cues to biological function. Trends Neurosci. **20**(12): 570–577.
104 Sadock BJ, Sadock VA (2005). Kaplan & Sadock´s Comprehensive Textbook of Psychiatry, Eight Edition. Lippikott Williams & Wilkins. Vol.I, pp. 1559–1718.
105 Saito M, Hori M, Obara Y, Ohizumi Y, Ohkubo S, Nakahata N (2006). Neurotrophic factor production in human astrocytoma cells by 2,5,6-tribromogramine via activation of epsilon isoform of protein kinase C. Eur J Pharm Sci. **28**: 263–271.
106 Simon NM, McNamara K, Chow CW, Maser RS, Papakostas GI, Pollack MH, Nierenberg AA, Fava M, Wong KK (2007). A detailed examination of cytokine abnormalities in Major Depressive Disorder. Eur Neuropsychopharmacol. **18**: 230–233.
107 Sofroniew MV (2005). Reactive astrocytes in neural repair and protection. Neuroscientist. **11**: 40–47.
108 Spiegel AM (1996). Defects in G protein-coupled signal transduction in human disease. Ann Res Physiol.**58**: 143–170.
109 Steel JL, Geller DA, Gamblin TC, Olek MC, Carr BI (2007). Depression, immunity, and survival in patients with hepatobiliary carcinoma. J Clin Oncol. **25**: 2397–2405.
110 Steele TA, Brahmi Z (1988). Phosphatidylinositol metabolism accompanies early activation events in tumor target cell-stimulated human natural killer cells. Cell Immunol. **112**: 402–413.
111 Tiraboshi E, Tardito D, Kasahara J, Morashi S, Pruneri P, Gennarelli M, Racagni G, Popoli M (2004). Selective phosphorylation of nuclear CREB by fluoxetine is linked to activation of CaM kinase IV and MAP kinase cascades. Neuropsychopharmacology. **29**: 1831–1840.
112 Torgersen KM, Vaage JT, Levy FO, Hansson V, Rolstad B, Tasken K (1997). Selective activation of cAMP-dependent protein kinase type I inhibits rat natural killer cell cytotoxicity. J Biol Chem. **272**: 5495–5500.
113 Trzonkowski P, Mysliwska J, Godlewska B, Szmit E, Lukaszuk K, Wieckiewicz J, Brydak L, Machala M, Landowski J, Mysliwski A (2004). Immune consequences of the spontaneous pro-inflammatory status in depressed elderly patients. Brain Behav Immun. **18**(2): 135–148.
114 Watson S, Gallagher P, Smith MS, Ferrier IN, Young AH (2006). The dex/CRH test – is it better than the DST? Psychoeuroendocrinology. **31**(7): 889–894.
115 Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HC, Joyce PR, Karam EG, Lee CK, Lellouch J, Lépine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK (1996). Cross-national epidemiology of major depression and bipolar disorder. JAMA **276**(4): 293–299.
116 Wettschureck N, Offermanns S (2005). Mammalian G proteins and their cell type specific functions. Physiol Rev. **85**(4): 1159–1204.
117 Whalen MM, Bankhurst AD (1990). Effects of β-adrenergic receptor activation, cholera toxin and forskolin on human natural killer cell function. Biochem J. **272**: 327–331.
118 Won CL, Oh IS (2000). cAMP- induced stellation in primary astrocyte cultures with regional heterogeneity. Brain Res. **887**: 250–258.
119 Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. Brain Behav Immun. **15**: 199–226.