THE NEW ARMENIAN MEDICAL JOURNAL
Vol.7 (2013), No 1, p.4-21

REVIEW OF LITERATURE

NEUROIMMUNE-ENDOCRINE SYSTEM DISORDERS IN DEPRESSION

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Received 9/29/2012; accepted in final form 12/25/2012

ABSTRACT

The review is dedicated to analysis of contemporary ideas on a role of neuroimmune-endocrine disorders in depression development. Here are presented peculiarities of disorders occurring in depression during processes of synthesis, release, transport and reception of noradrenaline, dopamine and serotonin and population of their pre- and postsynaptic receptors in various brain structures. Data on glutamate- and GABA-ergic system disorders are given here, including those on the level of N-methyl-D-aspartate and α-amino-propionic acid-glutamate receptors, in depression origin. Within the frames of cascading mechanism of immune-mediated alteration of glutamate-serotonin system in depression the role of pro-inflammatory cytokines is here observed, as well as contemporary ideas on neurosteroid and neurotrophic conceptions of depression pathogenesis. The research results on investigation (postmortem) of disorder peculiarities from the side of serotonin and dopaminergic brain systems (suicide victims) in depression are given separately. Besides, here are presented data on detection of Zn^2-enriched neurons in various brain structures, "zinc-enriched neurons", and on ability of Zn^{2+} releasing into the synaptic fissure to show antidepressant influence by modulating glutamate, glycine- and GABA-ergic synaptic neurotransmission, raising sensibility of 5-hydroxytryptamine $_{1A}$ and $_{2A}$ serotonin receptors and brain-derived neurotrophic factor level in brain. Data on peculiarities of neuroimmune-endocrine disorders in post-stroke depression and depression developing in Alzheimer's and Parkinson's diseases are considered here as well.

Keywords: *depression, suicide, neurodegenerative disease, monoaminergic neurotransmission, glutamate and GABA-ergic systems, neurosteroids, neurotrophins, zinc.*

*I*Predicted growth of depression cases in megascales is a reason of the boom arisen for the last decades in the field of its study in different aspects. Despite of progressively growing number of new generations of natural and synthetic origin antidepressants, most of them have side effects, and the cases of pharmacoresistant depression increase, thus, on the whole dictating a necessity of the new approaches in development towards pathogenetic therapy of depressive diseases.

According to WHO data, 5-10% of the world population suffer from depression. It is predicted that by 2020, on a global scale, depression will take the second place among human disabilities [*Geddes J., Butler R., 2001; Paykel E., 2006; WHO, 2006 a; b*]. Sufficiently large percent of people suffering from depressive disorders is registered also in the countries of European region [*Alonso J. et al., 2004; Kohn R. et al., 2004; Simon G. et al., 2004*]. Peculiarities of depression and suicidality have been marked in different populations, ethnical and psychosocial groups, as well as their age-related and gender differences [*Kafman M. et al., 2003; Wilmoth J., Chen P., 2003; Reynolds C. et al., 2006; Wadley V. et al., 2007; Kanchan T., Menezes R., 2008; Wang J. et al., 2008*]. The problem of depression among teenagers and young people becomes more and more actual [*Brent D., Birmaher B., 2002; Chang H. et al., 2008*]. It is estimated that frequency of depressive disorders among 14-16 year old schoolchildren is 15-20% having tendency to escalation [*Aalto-Setala T. et al., 2002; Zinn-Souza L. et al., 2008*]. There is also data on de-

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pression development in teenagers due to internet addiction [*Yen J. et al., 2008*]. It is established that depression prevalence index reaches 35-40% in the age group of 20-24s [*Korkeila J. et al., 2003; O'Herlihy A. et al., 2003; Sekoyan I.E., 2008*]. Starting from the middle of the last century there have been suggested different hypotheses on depression origin, the number of which grows steadily due to modern achievements in neurochemistry, neurophysiology, molecular biology, immunology, as well as the wide use of neurovisualisation and current methods of brain tissue metabolism.

Monoaminergic Brain System and Depression: Monoaminergic theory of depression origin formulated half a century ago still remains to be the most acceptable. Its competence is proved by results of the researches testifying that depression develops owing to serotonin-, noradrenalin- and dopaminergic neurotransmission deficit.

Successful development of research was promoted by the works dedicated to study transport and metabolism mechanisms, synaptic release, reverse uptake of serotonin, numerous (*over 15*) populations of 5-HT-receptors and their role in dopaminergic structure functioning in norm and depressive disorders [*Gerard C. et al., 1997; Barnes N., Sharp T., 1999; Branchek T., Blackburn T., 2000; Lucas G. et al., 2001; Roberts J. et al., 2002*]. After discovery of human polymorphism gene – serotonin carrier [*Heils A. et al., 1997; Smeraldi E. et al., 1998; Rausch J. et al., 2002; Smith G. et al., 2004; Serretti A. et al., 2005*], research intensification in this field promoted revealing interrelation of 5-HT_{A2} receptors with serotonin carrier and polymorphism gene of tryptophan-hydroxylase in real depression [*Du L. et al., 1998*].

The role of polymorphism gene of serotonin carrier in realization of effects produced by selective inhibitors of serotonin reverse intake antidepressants was revealed [*Arias B. et al., 2003; Kraft J. et al., 2007; Barton D. et al., 2008; Lotrich F. et al., 2008; Mehta D. et al., 2010*], as well as the new proofs were obtained on competence of brain "*serotonin vulnerability*" conception in depression, providing an important role of serotonin and tryptophan deficit in brain tissue in the genesis of depressive disorders [*Neumeister A. et al., 2006; Jans L. et al., 2007*].

Formulated dopaminergic hypothesis of depression development also found its acknowledgement **[***Mann J., Kapur S., 1995***]**. Thus, an essential role in depression pathogenesis was given to polymorphism gene of dopamine carrier [*Haeffel G. et al., 2007*] and its decreased ability to bind dopamine in synaptic formations of striatum [*Meyer J. et al., 2001*]. Peculiarities of dopamine β-hydroxylase gene in development of noradrenergic dysfunction in depression were also revealed [*Togsverd M. et al., 2008*]. It was established that one of the reasons for disbalance development in monoamine levels in brain tissue in depression was hyperactivity of monoamine oxydases [*Meyer J. et al., 2005*]. Characteristic features of neuronal responses in depression accompanied by catecholamines levels decrease in brain tissue were studied [*Hasler G. et al., 2008*]**.**

The role of disorders in brain noradrenergic systems was considered in occurrence of suicidal behavior in depression. There are marked disorders in brain noradrenergic systems at different stages of synthesis (tyrosine hydroxylase activity), release, noradrenaline reverse intake and its interaction with central α_2 and, especially, β_2-adrenoreceptor and with a running signaling cascade in depression [*Pandey G., Dwivedi Y., 2007; Belmaker R., Agam G., 2008*] (Figure 1).

Thus, it is necessary to consider established that mechanisms of deficit development of monoaminergic transmission in depressions are as follows: reduction of tryptophan content in presynaptic terminals, increase of mutation frequency of tyrosine hydroxylase (TPH-2) gene specific for brain tissue, increase of specific ligand-binding ability of MAO-A, lack of presynaptic 5-HT_{1B}-autoreceptors functioning, decrease of p11 level, sub-sensitiveness of serotonin 5-HT_{1A}-autoreceptors, polymorphism of gene of serotonin reverse intake transporter, rise of presynaptic α_2-adrenoreceptor sensitivity, inadequate response of G-protein to neurotransmitter signaling, reduction of cAMP, inositol and CREB level in brain.

Glutamate- and GABA-ergic Brain Systems and Depression: The significant role in depression pathogenesis is given to disorders of glutamate- and GABA-ergic brain systems, including activation of excite toxic mechanisms. Particularly, there has been revealed Ca^{2+}-glutamate cascade activation realized through population of N-methyl-D-aspartate (NMDA)- and α-amino-propionic-acid (AMPA)-glutamate receptors [*Calabresi P. et al., 2000; Javitt D., 2004; Gladding C. et al., 2009; Kapsalia F. et al., 2009; Rebola N. et al., 2010*]. It was detected that decrease in the level of NR_{2A} and NR_{2B} NMDA glutamate receptors subunits in prefrontal cortex was typical for depression [*Feyissa A. et al., 2009*]. It was determined that antagonists of NMDA- and AMPA-glutamate receptors had antidepressive effect, including the cases with pharmacoresistant forms of depression [*Barbon A. et al., 2006; Zarate C. et al., 2006; Bobula B., Hess G., 2008; Deakin J. et al., 2008; Diazgranados N. et al., 2010*].

The method of proton magnetic-resonance spectroscopy helped to reveal a reduction of glutamate/glutamine and GABA level in prefrontal cortex area of big hemispheres in depression [*Hasler G. et al., 2007*], decreased immunoreactivity of GABA-ergic neurons of frontal cortex to Ca^{2+}-binding proteins [*Rajkowska G. et al., 2007*].

Specific injury of GABA and glutamatergic structures [*Brambilla P. et al., 2003; Sanacora G. et al., 2004*] occurs in depression, including disorders of GABA- and glutamatergic transmissions in glial cortex structures [*Merali Z. et al., 2004 a; b; Choudary P. et al., 2005*]. At present GABA and glutamatergic systems are considered as targets in depression pharmacotherapy [*Kendell S. et al., 2005*].

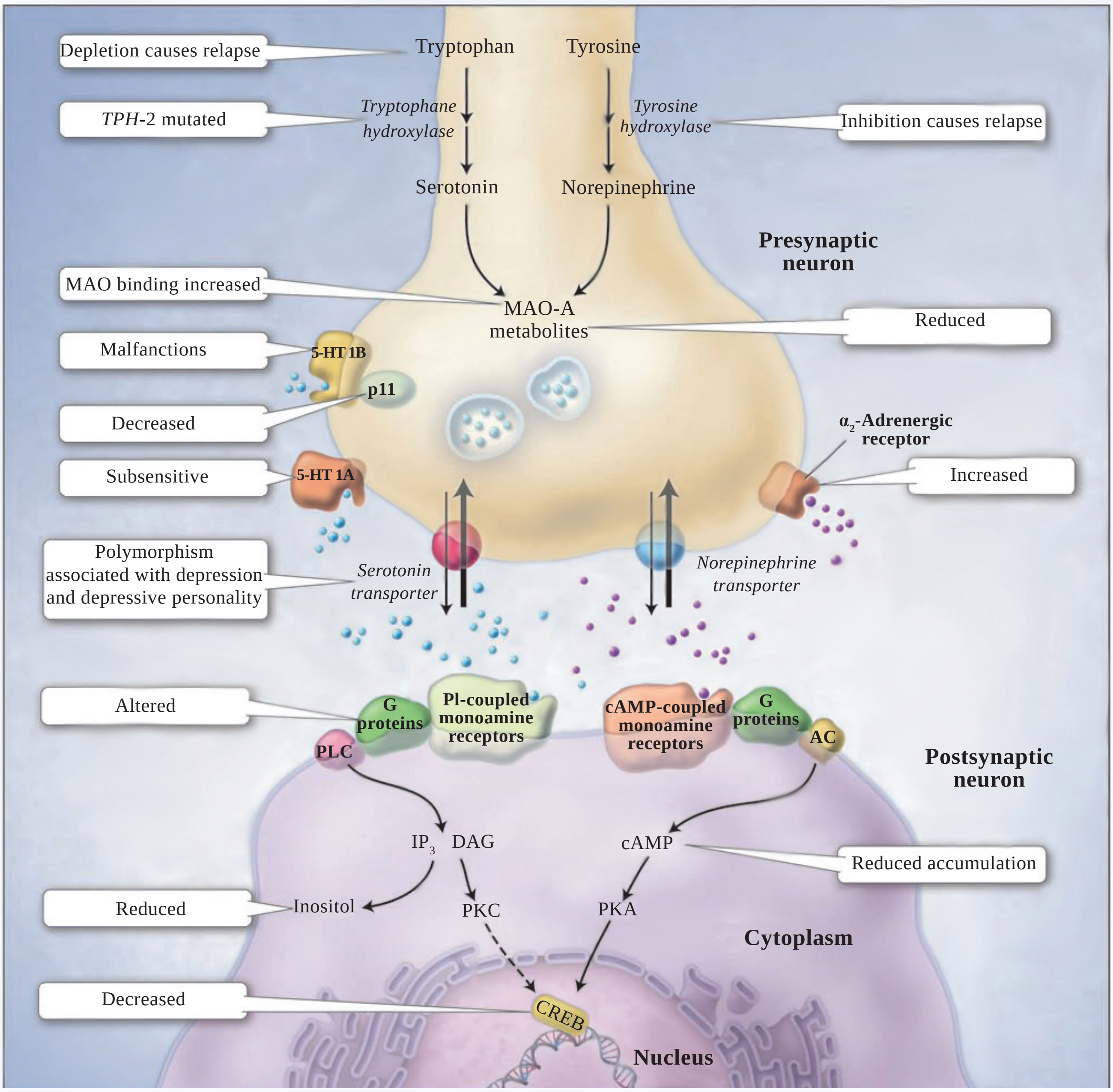

FIGURE 1. *Hypothetical scheme of monoaminergic neurotransmission disorders in depression.* [*Reprinted from* Belmaker R., Agam G., 2008.]

Neuroimmune-endocrine Mechanisms of Depression: According to modern ideas, the vital role in depression pathogenesis belongs to neuroimmune-endocrine disorders with involvement of hypothalamus-hypophysis-adrenal (HHA) glands axe and immune-mediated alteration of glutamate-serotonin system [*Anisman H. et al., 2008; Anisman H., 2009*].

Classical ideas and new proofs of HHA axe involvement in depression development were reviewed in detail [*Dunn A., 2000; Pariante C., Lightman S., 2008*], the corticosteroid concept of depression development was put forward [*Holsboer F., 2000*], and neuroendocrine mechanisms of antidepressant action were studied [*Schüle C., 2007*]. The role of superfluous release of corticotrophin releasing hormone (CRH) from neurons of hypothalamus paraventricular nucleus in depression genesis was revealed [*Raadsheer F. et al., 1994; Nemeroff C., 1996*] and the problem of dissociation of anxiogenic effect of CRH release discussed [*Merali Z. et al., 2004 b*]. Roles of CRH_1 and CRH_2 receptors in depression genesis [*Reul J., Holsboer F., 2002*] and effects of CRH_1 receptor antagonists were studied [*Holsboer F., Ising M., 2008*].

In depression a decrease of glucocorticoid receptors sensibility towards endogenous and exogenous ligands was marked [*Modell S. et al., 1997*], as well as the deficit in content of neurosteroid receptors in different brain structures revealed [*Boyle M. et al., 2005*]. Direct proofs were obtained on competency of the so-called "*hypothalamus – hypophysis – adrenal glands (cortisol)*" hypothesis of stress-induced depression development, which was based on the phenomenon of abnormal reaction to cortisol and data on cortisol high concentration ability to inhibit formation of brain-derived neurotrophic factor (BDNF) in hippocampus [*Carroll B. et al., 2007; Castrén E. et al., 2007*].

The neurotrophic concept of depression was formulated on the basis of data specifying deficiency role of BDNF and its receptors in hippocampus in depression pathogenesis [*Altar C., 1999; Martinowich K. et al., 2007*], ability of some antidepressants to increase immunoreactivity of hippocampus BDNF [*Chen B. et al., 2001; Louis C. et al., 2006*] and, at last, presence of antidepressive effect in BDNF [*Shirayama Y. et al., 2002; Hoshaw B. et al., 2005*]. Amongst depression development mechanisms a valuable role was dedicated to alteration of peptidergic brain system, including participation of CRH, arginine-vasopressin, B neuromedin, P and BDNF substances [*Nemeroff C., 2008*].

The conception on cytokine role in the mechanisms of depression development is worth mentioning within the frames of cascade mechanism of neuroimmune-endocrine disorders; its competency was proved by data on immune-mediated alteration of "*glutamate – serotonin*" system [*Dantzer R. et al., 1999; Irwin M., 1999; Anisman H., Zacharko R., 2001; Hayley S. et al., 2005; Miller A., Raison C., 2006; Spalletta G. et al., 2006*].

It was shown that pro-inflammatory cytokines (IL-2, g-interferon, TNFα,) together with indolamine-2,3-dioxigenase induction, accompanied by amplified metabolic serotonin degradation in brain tissue, increased kynurenine monoxigenase activity, thus promoting formation of superfluous quantities of quinolinic acid appearing as a strong agonist of glutamate NMDA-receptors [*Wichers M., Maes M., 2002; Müller N., Schwarz M., 2007*]. The ability of pro-inflammatory cytokines to increase resistance of neurosteroid receptors towards endogenous ligands was established in depression [*Manji H. et al., 2001; Pace T. et al., 2007; Anisman H., 2009*] (Figure 2).

Thus, it was established that stressors and cytokines may promote several common neurochemical changes, and it was suggested that they might act synergistically in affecting some neurochemical processes. Moreover, stressors and cytokines might result in the sensitization of neurochemical processes, resulting in exaggerated responses to subsequent challenges. Both cytokines and stressors, as depicted in Figure 2, increase the release of CRH in hypothalamic and extrahypothalamic sites, although, in case of stressors, this outcome might involve activation of bombesin-like peptides (neuromedin B and gastrin-releasing peptide). In addition to activating hypothalamic–pituitary–adrenal function, CRH might influence serotonin (5-HT) processes, and γ-aminobutyric acid receptor A (GABA A) activity might act as a mediator in this regard. The 5-HT variations (as well as those of other amines) might influence depression directly or through other processes. In this regard, an alternative, although not necessarily mutually exclusive, the pathway involves cytokine/stress activation of either nuclear factor-κB (NFκB), mitogen-activated protein (MAP) kinases or janus kinase/signal transducer and transcription (JAK-STAT) activator pathway signalling. These would influence oxidative or apoptotic mechanisms, leading to altered growth factor expression (e.g., BDNF), again favouring impaired neuroplastic processes and culminating in major depression.

Zinc and Depression: Modulatory role of Zn^{2+} in the mechanisms of glutamate- and serotonin-ergic neurotransmission and depression pathogenesis was determined.

It is known that zink appears as a structural component and cofactor of some enzymes regulating processes of intracellular signaling [*Takeda A., 2000*]. In mammalian brain Zn^{2+} exists in the associated form with proteins (95%), the specific zinc pool is localized in presynaptic vesicles. Zinc-enriched neurons (ZEN) are localized in various brain areas rich with glutamatergic and glycinergic structures, including amygdala and hippocampus [*Frederickson C., Moncrieff D., 1994; Frederickson C. et al., 2000*].

ZNT3-protein was detected, secreted, purified and identified to control the level of Zn^{2+} in synaptic vesicles [*Linkous D. et al., 2008*]. Activation role of p75NTR zinc-trigger in the mechanisms of brain neuroprotection was established [*Lee J. et al., 2008*].

Zinc ability to penetrate through hematoencephalic barrier (HEB) was detected as well [*Takeda A., Tamano H., 2009*]. Zn^{2+} released into a synaptic cleft was shown to modulate glutamate-, glycine- and GABA-ergic synaptic transmission, to appear a trigger for mGluR-receptor mediated metabotropic signaling realized by binding with Zn^{2+}-sensible receptors of hippocampus [*Laube B., 2002; Mocchegiani E. et al., 2005*]. It was detected that Zn^{2+} action upon NMDA-glutamate receptors might be realized by two mechanisms: potentially independent, allosteric inhibition and potentially dependent inhibition at the expense of the open channel blocking effect [*Paoletti P. et al., 2009*]. Zinc was also shown to be the modulator of AMPA-glutamate receptors inducing their modulation independent from

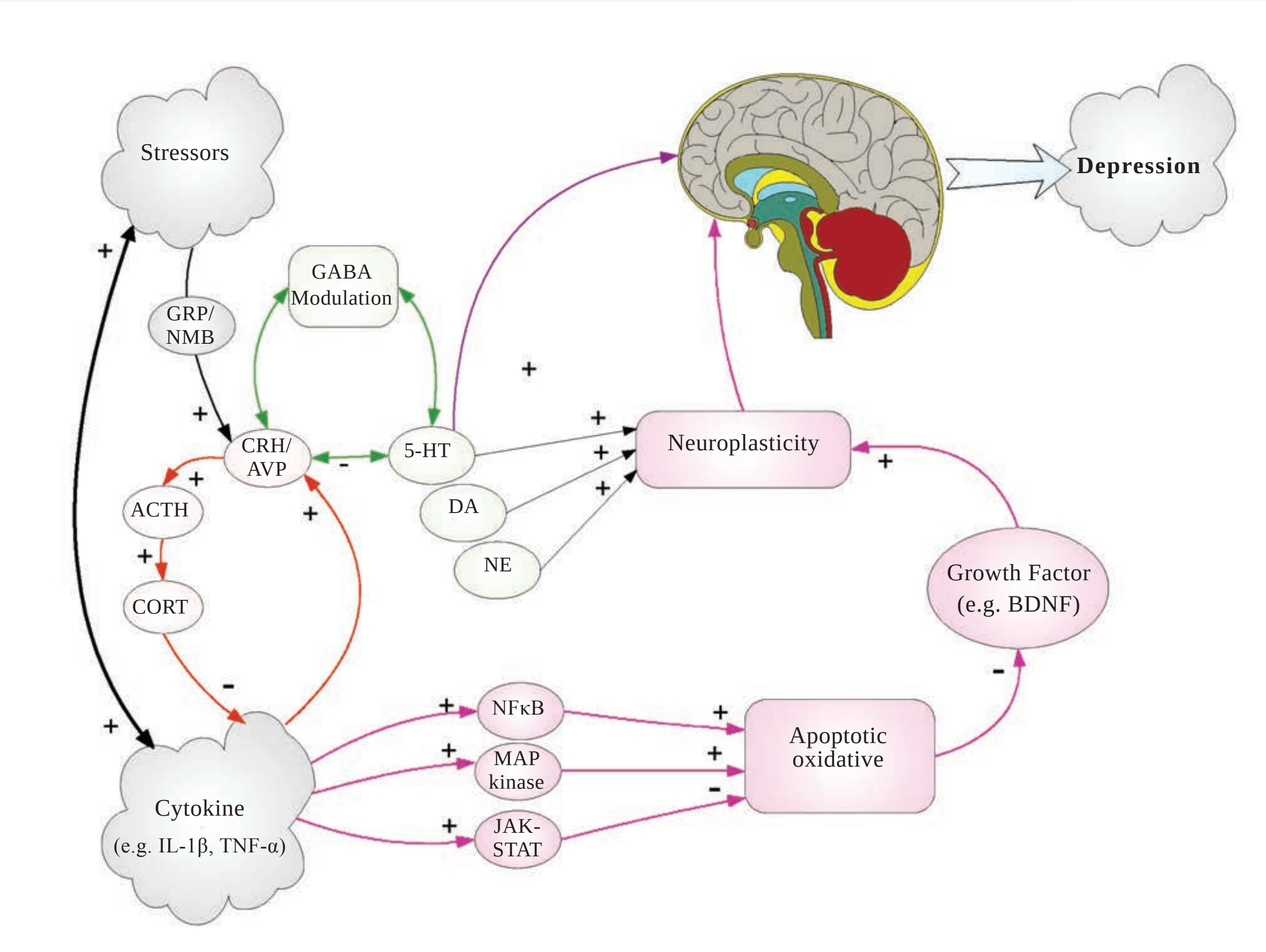

FIGURE 1. Working model showing potential routes, by which stressors and cytokines could influence depressive state. Reprinted from Anisman H., 2009.

NMDA-receptors [*Besser L. et al., 2009*].

Results of the first clinical research witnessed to low level of Zn^{2+} in blood plasma of patients with depression [*McLoughlin I., Hodge J., 1990; Maes M. et al., 1994; Nowak G. et al., 1999*]. The negative correlation between Zn^{2+} concentration in blood plasma and rate of depression intensity was revealed [*Schlegel-Zawadzka M., 2000; Wojcik J. et al., 2006*]. Data on Zn^{2+} role in both depression development and normalization of zinc levels in blood plasma of patients in pharmacotherapy became the basis for combined application of zinc with antidepressants [*Maes M. et al., 1997*]. The effectiveness of adding zinc in pharmacoresistant and unipolar depression was shown on the background of pharmacotherapy by tricyclic antidepressants and selective inhibitors of serotonin reverse intake [*Nowak G. et al., 2003; Siwek M. et al., 2009*].

As established, the inhibiting effect of zinc upon glutamate signaling realized by NMDA-receptor blockade [*Poleszak E. et al., 2008; Szewczyk B. et al., 2010 a*] and modulation of AMPA-glutamate receptors underlay its antidepressive effects; moreover, it was shown that AMPA-receptor antagonists diminished zinc antidepressive effect [*Szewczyk B. et al., 2010 b*]. The synergism between Zn^{2+} and inhibitors of reverse serotonin and noradrenalin reverse intake was revealed [*Szewczyk B. et al., 2002; Rosa A. et al., 2003*].

Preliminary injection of *inhibitor of serotonin synthesis* (pCPA), *antagonist of 5-HT$_{1A}$ receptors* (WAY 1006335) and irritant serine as *antagonist of 5-HT$_{2A/C}$ receptors* reduced the antidepressive effect of zinc [*Szewczyk B. et al., 2009*]. Long-term treatment of depression by zinc was accompanied by an increase of sensibility of 5-HT$_{1A}$ and 5-HT$_{2A}$ serotonin receptors in hippocampus and frontal cortex [*Cichy A. et al., 2009*]. The role of BDNF in depression pathogenesis and treatment was estimated [*Siuciak J. et al., 1997; Duman R., 2004; Schmidt H., Duman R., 2007*]; it was also revealed that chronic injection of Zn^{2+} high doses promoted the rise of BDNF level in cortex, while low doses increased the same factor in hyppocampus [*Nowak G. et al., 2004; Sowa-Kucma M. et al., 2008*] (Figure 3).

Characteristic Peculiarities of "Suicide Victims" Brain in Depression: taking into account the growing percent of suicide behaviour and complete suicide among people with depression, especially those of young and teenage **[***Bertole J., Flischman S., 2002; Luoma J. et al., 2002; Suicide prevention in Europe, 2002; Shaughnessy L. et al., 2004; WHO, 2006 b; Shoenherr N., 2007; Suicide, 2007; USA Suicide, 2007*], a separate direction of the research was dedicated to *post mortem* investigation of brain peculiarities in suicide victims in depression. The great relative density in this plan belonged to research results of disorder peculiarities from the side of brain monoaminergic systems [*Stockmeier C. et al., 1997; Bligh-Glover W. et al., 2000; Mann J. et al., 2000; Arango V. et al., 2003; Valdizán E. et al., 2010*]. Thus, in brains of suicide victims with depression there were revealed disorders from the side of 5HT$_{1A}$-receptors, binding abilities of serotonin carrier and expression of mRNA serotonin transporter [*Arango V. et al., 2001*].

The suicide was associated with the gene of polymorphism of 5HT$_{1B}$-receptors [*Nishiguchi N. et al., 2001; Rujescu D. et al., 2003; Stefulj J. et al., 2004*], with disorders of binding places of 5-HT$_{2A}$- and 5HT$_4$-receptors of serotonin in hippocampus, disorders of intracellular signaling system, including secondary messengers – IP$_3$ and cAMP [*Rosel P. et al., 2000; 2004*], growth in cortical structures realized by mRNA expression of 5-HT$_{2C}$-receptors of serotonin [*Simmons M. et al., 2010*]**,** decrease of tryptophan-hydrolase activity in dorsal nucleus of stitch [*Boldrini M. et al., 2005*] and mutation of gene of tyrosine-hydrolase TPH-2 specific for cerebral tissue [*Lopez de Lara C. et al., 2007*].

A reduction of binding places of dopamine re-

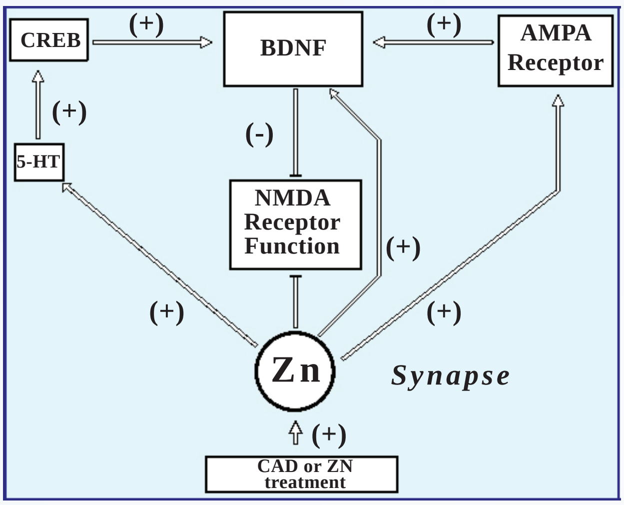

FIGURE 3. *A simplistic representation of the mechanism linked to antidepressant-induced increases intersynaptic zinc (Zn) concentration. Reprinted from Szewczyk B. et al., 2010.*

verse intake and lower sensibility of D_2-receptors of dopamine was recorded in *caudate nucleus* in brain of suicide victims with depression [*Allard P., Norlén M., 1997; 2001*]. The decreased activity of phosphatidyl inositol 3-kinase and PTEN phosphatase was marked in prefrontal cortex [*Karege F. et al., 2011*]. In monoamine-containing granules of suicide victims' brain in depression there was observed a rise of immune reactivity of corticotropin releasing hormone [*Austin M. et al., 2003*]. Data was reported on disorders in the expression system of specific regulatory and catalytic subunits of protein kinase **A**, binding places with cAMP and activity of A protein kinase in prefrontal cortex of suicide victims' brain [*Dwivedi Y. et al., 2002; 2004*].

Poststroke Depression: Post-stroke depression and its comorbidity with cognitive disorders of predemented and demented levels were (and still remain) considered one of the most vital sociomedical problems [*Narushima K. et al., 2003; Verdelho A. et al., 2004; Bruce J. et al., 2008; Donovan N. et al., 2008*]. The oppressing action of post-stroke depression on cognitive function was established [*Stewart R., 2004; Brodaty H. et al., 2007*]; furthermore, post-stroke depression was considered a risk factor of dementia development [*Whyte E., Mulsant B., 2002; Hachinski V., 2003; Robinson R., 2003; Hackett M. et al., 2005; Williams L., 2005; Tharwani H. et al., 2007; Chen R. et al., 2008; Thomas S., Lincoln N., 2008; Cape J. et al., 2010*].

In formation of post-stroke dementia the considerable role was given to serotonin and multiple populations of its receptors, glutamatergic terminals, NMDA- and AMPA-receptors of glutamate, dopaminergic mediation, as well as to their neurosynaptic clusters and disorders of NMDA-transmission [*Homayoun H. et al., 2004; Rowland L. et al., 2005; Tsukada H. et al., 2005; Grosjean B., Tsai G., 2007; Rebola N. et al., 2010*].

As established, the important role in development of depression, as well as in cognitive disorders, belongs to homocysteine [*Bottiglieri T. et al., 2000; Tiemeier H. et al., 2002; Folstein M. et al., 2007; Kim J. et al., 2008*]. Simultaneously, results of prospective research enable to formulate ideas on depression as one of the modified risk factors of stroke development [*Hachinski V., 2007; Rabi-Zikić T. et al., 2007; Thomas S., 2007; Bos M. et al., 2008; Zhang J. et al., 2008*].

Depression in Alzheimer's Disease (AD): Several researchers suggested to consider depression as a prodrome or peculiar debut of AD [*Copeland M. et al., 2003; Modrego P., 2009; Wilson R. et al., 2010*]. Particularly, the analysis of clinical observation results of 30 Centers in USA involved in the investigation of AD indicated depression as a risk factor for average cognitive disorders in AD [*Green R. et al., 2003; Steenland K. et al., 2012*].

According to forecast, the presence of depression in AD is an adverse sign for activity limitation in daily life, physical inability and fast death. Results of pathomorphological investigations testified to low content of noradrenaline (in the region of *locus coeruleus*), serotonin (in the region of dorsal *raphe nuclei*) and dopamine (in *substantia nigra*) in brain of patients with AD suffering from depression [*Devenand D. et al., 2002*].

The release of proinflammatory cytokines by activated microglia was considered one of the supposed mechanisms of depression development in AD [*Barber R., 2011*]. It is important to mark that according to modern ideas, depression appeared risk factor for development of cognitive disorders of dement and nondement level [*Austin M. et al., 2001; Mitchell A., 2005; Dotson V. et al., 2010; Saczynski J. et al., 2010; Wesolowski K., 2010*].

Depression in Parkinson's Disease (PD): Depression is one of the most frequent cases of affective disorders in PD. According to different authors, depression was observed in 40-50% of patients with PD [*Schrag A., 2005; Weintraub D., 2005; Storch A. et al., 2008; Dissanayaka N. et al., 2011; Schwarz J. et al., 2011*]. Depression is often hyperdiagnosed or not diagnosed in PD; this latter is connected with the presence of some similar clinical manifestations in depression and PD [*Burn D., 2002*]. Depression might occur at any stage of PD, but sometimes (30%) preceding its first clinical motor manifestations (hypokinesia, rigidity, rest tremor) [*Rojo A. et al., 2003; Sawabini K., Watts R., 2004*].

For the last years an increased interest towards the problem of depression in PD has been explained by generality of disorders from the side of mesolimbic and mesocortical dopaminergic structures developing with the mentioned pathologies [*McDonald W. et al., 2003; Remy P. et al., 2005; Lieberman A., 2006; Reijnders J. et al., 2008*], as well as disorders in processes of synthesis, release and reverse intake of some neuromediators, first of all, noradrenaline and serotonine modulating status of frontal striatal rings and limbic structures

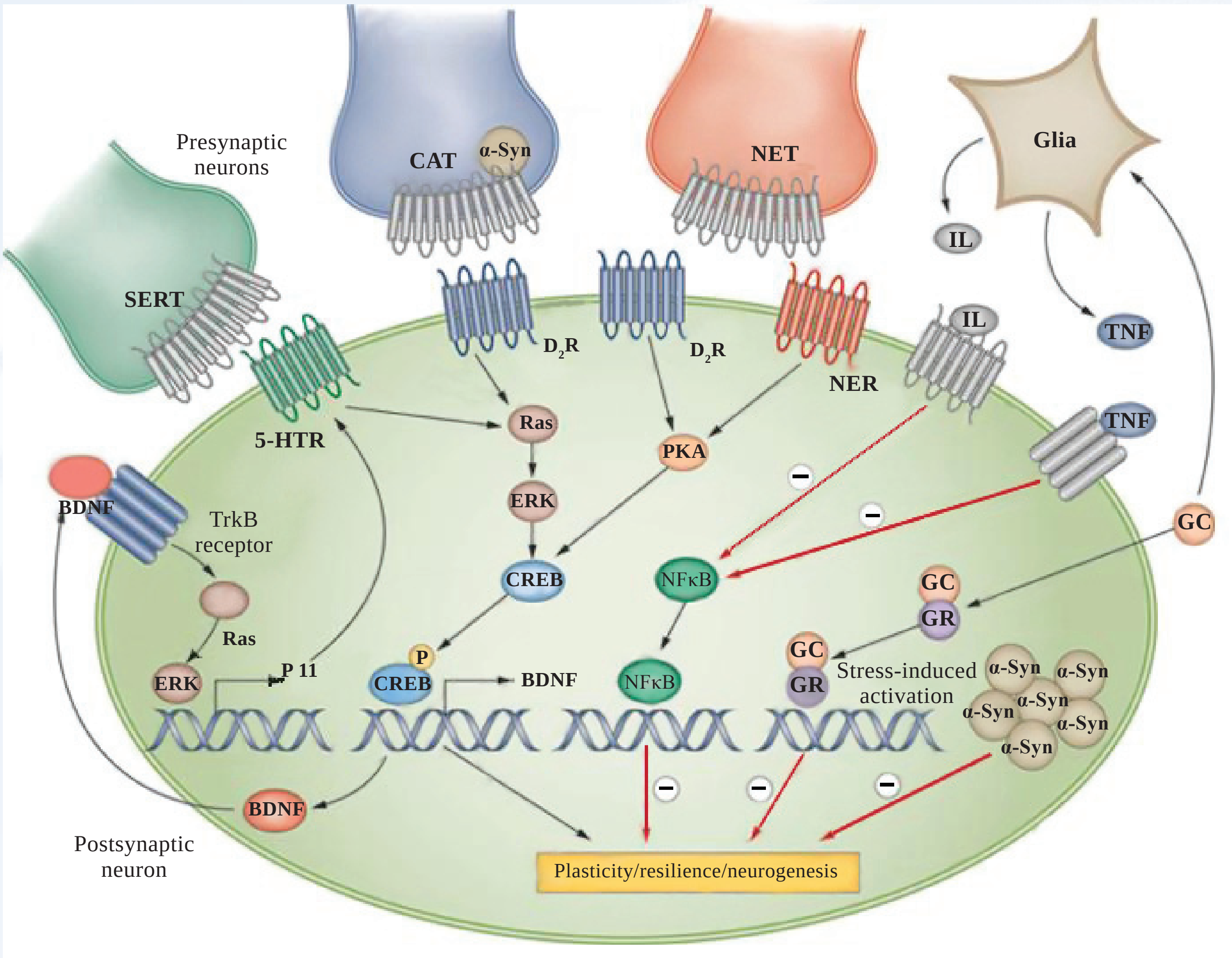

FIGURE 4. Downregulation of monoamines, partuiculary dopamine and noradrenaline, might underlie depression in patients with PD. [Reprinted from Aarsland D. et al., 2012].

[*Troster A. et al., 2000; Brooks D., Doder M., 2001; Yamamoto M., 2001; Ehrt U. et al., 2006*]. Particularly, an increase in ability of selective carrier to bind and transport serotonin was established by positron emission tomography (PET) in brain of patients with PD having clinical manifestations of depression [*Boileau I. et al., 2008*]. Patomorphological investigations revealed that in combination of PD and depression there occured expressed changes from the side of noradrenergic structures of *locus coeruleus* and serotoninergic structures of *raphe nuclei* [*Lemke M. et al., 2004*]. There are data testifying that treatment of PD patients with application of L-DOPA was one of the factors promoting depression development in PD [*Eskow Jaunarajs K. et al., 2010*] (Figure 4).

Thus, as established, stimulation of monoamine receptors activates several signaling cascades and eventually leads to increase of BDNF. This mediator supports cellular plasticity, resilience and neurogenesis, and drives the expression of the monoamine receptor adaptor protein p11, which, in turn, increases the efficacy of some 5-HT receptors at the neuronal surface. Large amounts of glucocorticoid receptors and inflammatory markers (such as TNF and interleukins) are released from glial cells and act *via* transcription factors, such as the glucocorticoid receptor and NFkB, to exert a negative influence on neuronal plasticity, resilience and neurogenesis. Increased α-synuclein load could increase the risk of depression by negatively affecting dopamine transmission, neuroplasticity and regeneration.

5-HT	5-hydroxytryptamine or serotonin
5-HTR	5-HT receptor
AC	adenylate cyclase
ACTH	adrenocorticotropic hormone
AMPA	2-amino-3-propanoic acid α-amino-propionic acid receptor
AVP	arginine vasopressin
BDNF	brain-derived neurotrophic factor
CAD	conventional antidepressants
cAMP	cyclic adenosine monophosphate
CORT	cortisol
CREB	cAMP response element-binding protein
DA	dopamine
DR	dopamine receptor D
DAT	dopamine active transporter
DAG	diacylglycerol
ERK	extracellular signal-related kinase
G protein	GTP-binding protein (G protein)-coupled receptors
GC	glucocorticoid
GR\	glucocorticoid receptor
GRP	gastrin-releasing peptide
IL	interleukin
IP_3	inositol triphosphate
MAO-A	monoamine oxidase A.
NE	norepinephrin
NER	norepinephrine receptor
NET	norepinephrine transporter
NFκB	nuclear factor κB
NMB	neuromedin B
NMDA	N-methyl-D-aspartate receptor
p11	selectively bound to the serotonin receptor subtype $5HT_{1B}$
PD	Parkinson disease
PKA	protein kinase A
PKC	IP_3 and DAG activate protein kinase C
PLC	phospholipase C
SERT	sodium-dependent serotonin transporter
TNF	tumor necrosis factor
TPH-2	brain-specific form of tryptophan hydroxylase
TrkB	BDNF/NT-3 receptor
α-syn	α-synuclein (non A4 component of amyloid precursor)

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