We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Anti-Stress Effects of Mood Stabilizers and Relevance to Their Therapeutic Actions

Young-Ki Chung and Seungmin Yoo

*Department of Psychiatry, Ajou University School of Medicine
South Korea*

1. Introduction

Bipolar disorder proves to be a far more serious mental illness than previously thought due to high suicide rate, great functional impairments, and chronicity (Belmaker, 2004; Post et al., 1996). In patients with bipolar disorder, reduction of volume in specific brain areas has consistently been found (Drevets et al., 1997). Although pathophysiology of bipolar disorder is far from being clear, alterations in neuroprotective and neurotrophic signaling cascades are implicated in pathophysiology of bipolar disorder (Schloesser et al., 2008).

The original concept of the mood stabilizer was the agent that was effective in treating acute manic episodes and preventing their relapses, thus “stabilizing” the manic pole of bipolar disorder (Stahl, 2008). More recently, the concept of mood stabilizer has been broadened to include any drug to treat bipolar disorder (Stahl, 2008). Lithium and valproate are two of the most prominent drugs approved by the United States Federal Food and Drug Administration (FDA) used for the treatment of bipolar disorder. Since John Cade discovered the efficacy of lithium in the control of acute manic episode in 1948 (Cade, 1949), lithium has been a prototypic mood stabilizer. Lithium has also been found to be effective for the prevention of recurrent manic and depressive episodes and for augmenting the activity of classical antidepressants in some depressed patients (Baldessarini et al., 1999). Anticonvulsant mood stabilizers, of which structures are totally unrelated to lithium, are also efficacious for the treatment of bipolar disorder. However, despite the long history of use for the treatment of bipolar disorder, the mechanism of actions of mood stabilizers still remains obscure.

Mood stabilizers are known to possess neuroprotective and neurotrophic properties. It is well known that representative mood stabilizers, lithium and valproate regulate multiple target molecules in neuroprotective and neurotrophic signaling cascades. Major signaling cascades regulated by mood stabilizers are brain derived neurotrophic factor (BDNF) and extracellular signal-regulated kinase (ERK) pathways, glycogen synthase kinase-3 (GSK-3) mediated pathway, and regulating pathways for bcl-2 expression (Manji et al., 2000; Shaltiel et al., 2007). In addition, regulation of arachidonic acid cascade by mood stabilizers is considered to be another common mechanism of action of mood stabilizers (Rao et al., 2008).

Psychosocial stress is a predisposing and precipitating factor to mood disorders like depression and bipolar disorder. Psychosocial stress affects brain functions profoundly and stress response is mediated through interactions between brain areas implicated in pathophysiology of mood disorders (McEwen, 2004). Psychosocial stress, for example, contributes to depressive and anxious symptoms in patients with affective illness (Caspi et al., 2003; Hammen, 2005; Hammen et al., 2004; Melchior et al., 2007). Environmental and psychological stressors can recapitulate biochemical, structural, and behavioral aspects of depressive illness in laboratory animals (Pittenger & Duman, 2008). Substantial evidence indicates that neural plasticity induced by depression and chronic stress share common features. However, antidepressant treatment has shown to produce opposing effects to those induced by stress (Pittenger & Duman, 2008). Mood stabilizers also prevent stress-induced neural plasticity (Bachmann et al., 2005; Bourin et al., 2009). Moreover, external stress enhances apoptosis by decreasing antiapoptotic and increasing proapoptotic molecules (Kubera et al., 2011). These molecules are also the targets of mood stabilizers.

In the context of these overlapping signaling cascades involved in bipolar disorder, actions of mood stabilizers, and stress effect it is conceivable to infer that protection of stress-induced neural plasticity contributes to the mood stabilizing effect. In this chapter, protective effects of mood stabilizers against stress-induced neural plasticity (anti-stress effects) and their relevance to therapeutic effects will be discussed. For neuroprotective and neurotrophic properties of mood stabilizers, readers can refer to numerous excellent papers elsewhere.

2. Preventive effect of mood stabilizers on stress induced structural plasticity

Preventive effects on stress-induced structural plasticity seems to be centered on lithium, so in this section, stress-prevention effect will be focused on lithium.

2.1 The effect of lithium on structural plasticity in the hippocampus and prefrontal cortex

Stress effects on the brain have been most extensively studied in the hippocampus. The hippocampus is one of the key structures of the brain mediating the stress response. It has the highest density of stress hormone receptors, glucocorticoids and mineralocorticoids receptors in the brain with potent inhibitory influence on the activity of the hypothalamic-pituitary-adrenal axis. Morphology and functions of the hippocampus are altered by acute or chronic stress (Brunson et al., 2003; Buwalda et al., 2005; Mirescu & Gould, 2006). The morphological alterations and functional impairments of the hippocampus are observed in a number of mental illnesses such as mood disorders, posttraumatic stress disorder, schizophrenia, and Alzheimer's disease (DeCarolis & Eisch, 2010). Sustained exposure to stress or glucocorticoids (GCs) leads to structural remodeling of the hippocampus with impairments in the performance of hippocampal-dependent cognitive functions (de Quervain et al., 1998; Magarinos & McEwen, 1995).

This structural remodeling effect is best studied in the CA3 region of the hippocampus. Sousa et al. (2000) reported that chronic stress or sustained GCs treatment induces structural remodeling in the CA1 as well as CA3 region with impairments in hippocampal-dependent

learning and memory functions. Reduction in the length and branch point of apical dendrites in the CA3 was observed following various types of stress. Daily restraint stress for 21 days or GCs exposure led to atrophy and the retraction of apical dendrites of CA3 pyramidal neurons in the rodent. Exposure to chronic psychosocial stress also resulted in structural remodeling of pyramidal neurons in the CA3 (Magarinos et al., 1996). This type of stress-induced structural plasticity is reversible because disrupted cellular morphology is slowly restored after cessation of stress without actual cell loss. Stress-induced dendritic atrophy in CA3 is mediated through decreased glucose uptake, increased glutamate and Ca^{2+} excitotoxicity, and decreased BDNF expression (Duman et al., 1999).

Chronic restraint stress results in the similar structural remodeling in the medial prefrontal cortex (mPFC) to that observed in the CA3 region of the hippocampus (Cook & Wellman, 2004; Radley et al., 2004). However, the apical dendritic atrophy following chronic stress is observed in the mPFC, but not in the orbital cortex (Liston et al., 2006), which suggests regional specificity of stress effect. Stress induces dendritic spine loss and altered patterns of spine morphology in the PFC in young rats, but not in aged rats (Bloss et al., 2011).

Lithium was found to prevent stress-induced dendritic atrophy of CA3 pyramidal neurons. Wood et al. (2004) reported that concomitant lithium treatment to rats prevented apical dendritic atrophy of CA3 pyramidal neurons caused by the exposure to restraint stress for 21 days with prevention of stress induced glutamatergic activation such as increase in glial glutamate transporter-1 mRNA expression and phosphorylation of cAMP response element binding protein (CREB) in the hippocampus. Alterations in cAMP signaling are implicated in mood disorders including bipolar disorder (Blendy, 2006; Karege et al., 2004). However, lithium treatment had no effect on dendritic morphology in non-stressed rats. Taken together, it is conceivable that lithium's ability in preventing stress-induced dendritic remodeling and increased phosphorylation of CREB may contribute to its mood stabilizing efficacy.

2.2 The effect of lithium on structural plasticity in amygdala

Prolonged stress exposure induced increase in dendritic length and branching of principal cells in the amygdala, which is in contrast to dendritic remodeling found in the hippocampus and medial prefrontal cortex (Vyas et al., 2002). This stress-induced dendritic hypertrophy in the amygdala is associated with increased anxiety-like behavior (Vyas et al., 2006). Increase in the size and function of the amygdala was demonstrated in depression (Drevets, 2003). Functional and structural abnormalities in the amygdala have been implicated in bipolar disorder (Garrett & Chang, 2008). Increased amygdala activity was observed in manic and euthymic bipolar patients during emotional discrimination tasks (Yurgelun-Todd et al., 2000). The preventive effect of lithium on stress-induced dendritic remodeling was demonstrated in the amygdala as well. Johnson et al. (2009) investigated the stress effect and lithium's effect on the dendritic morphology in the amygdala using the same study paradigm of Wood et al. (2004). They found that chronic lithium treatment prevented the stress-induced (restraint stress for 21 days) increase in dendritic length and branching of principal pyramidal neurons in the basolateral amygdala. However, like pyramidal neurons in CA3, lithium had no effect on dendritic morphology of the principal cells in the amygdala in non-stressed animals. This finding also suggests a specificity of neuroprotective action of lithium against stress.

2.3 The protective effect of lithium on stress-induced structural remodeling involves stabilization of glutamatergic activation

Lithium's preventive effect on dendritic morphology is thought to be mediated at least by the decrease and stabilization of the stress induced glutamatergic activation. Several lines of evidence support this notion. First, the dendritic remodeling by chronic stress in the CA3 area was prevented with N-methyl-D-aspartate (NMDA) antagonist (Magarinos & McEwen, 1995) or dilantin which reduces glutamate release (Watanabe et al., 1992). In addition, dendritic atrophy of pyramidal neurons in the mPFC which occurs during restraint stress was prevented by the administration of a competitive NMDA antagonist, ± 3 -(2-carboxypiperazin-4yl) propyl-1-phosphonic acid (CPP) (Martin & Wellman, 2011). Second, stress elevates extracellular glutamate level, thus facilitating glutamate signaling in the limbic brain. Chronic restraint stress, not acute stress, increases glutamate release and uptake in the hippocampus (Fontella et al., 2004; Lowy et al., 1993). Acute stress elevates extracellular glutamate level in the amygdala (Reznikov et al., 2007) and in the medial PFC (Moghaddam et al., 1994). Third, lithium is known to suppress glutamatergic signaling. Lithium treatment increases glutamate uptake into synaptosomes (Dixon & Hokin, 1998) and stimulates glutamate metabolism (Marcus et al., 1986). Fourth, lithium decreases the level of phosphorylation of NR2B subunit of NMDA receptor, thus suppressing the activity of NMDA receptor (Hashimoto et al., 2002). Lamotrigine which is an effective anticonvulsant mood stabilizer reduces glutamate release (E.S. Brown et al., 2010). These findings suggest that one of the key mechanisms of the therapeutic effect of lithium is the prevention of stress-induced dendritic remodelling by the stabilization of glutamate levels (Johnson et al., 2009).

3. The preventive effects of mood stabilizers on stress induced impairment in neurogenesis

3.1 Neurogenesis in the hippocampus

Neurogenesis in the adult brain has been found in most vertebrates including humans (Eriksson et al., 1998; Gould et al., 1999). Adult neurogenesis mainly occurs in the subgranular zone of the dentate gyrus in the hippocampus and subventricular zone of the ventricle wall (DeCarolis & Eisch, 2010). However, adult neurogenesis in the hippocampus is restricted to the subgranular zone of the dentate gyrus. Some researchers (Henn & Vollmayr, 2004) argue that impaired adult neurogenesis in the dentate gyrus may contribute to the reduced hippocampal volume in depressed patients although the contribution of neurogenesis in the dentate gyrus to the total volume of the hippocampus is considered very low in rodents and primates (Cameron & McKay, 2001; Kornack & Rakic, 1999). Adult neurogenesis is a multistep process. A brief description of adult neurogenesis is presented in this section (see Boku et al., 2010; Lucassen et al., 2010).

In the precursor cell phase, radial glia-like stem cells in the subgranular zone are, through transit amplifying cells, transformed to neural progenitor cells. Cell proliferation increases the number of neural progenitor cells. Cell fate determination is also believed to occur in transit amplifying cells. In the postmitotic cell phase progenitor cells are transformed to immature neurons in which axonal and dendritic extensions are initiated. These immature neurons are to be eliminated dramatically. This elimination process is apoptotic, NMDA

receptor-mediated and input dependent (Biebl et al., 2000; Kuhn et al., 2005; Tashiro et al., 2006). Surviving immature neurons migrate to the granular cell layer. Immature neurons mature with the maturation of dendritic spines. Newly formed mature neurons are finally incorporated to the hippocampal circuitry with projections to the CA3 neurons through mossy fiber pathway. These newborn granule cells have lower threshold for the induction of long term potentiation (LTP) and their survival depends on input dependent activity (Schmidt-Hieber et al., 2004). If integration to the pre-existing network does not occur, newborn cells are rapidly eliminated by apoptosis (Dayer et al., 2005).

3.2 The effect of mood stabilizers on stress-induced inhibition of neurogenesis in the hippocampus

Adult neurogenesis in the hippocampus is regulated by various environmental factors and age (J. Brown et al., 2003; Kempermann et al., 1997). With increasing age, adult neurogenesis rapidly declines (Manganas et al., 2007). Factors regulating adult neurogenesis include stress, exercise, dietary restriction, and an enriched environment. Stress is a potent negative regulator of adult neurogenesis (Boku et al., 2010). Exposure to both psychosocial and physical stressors inhibits one or more subphases of adult neurogenesis (Czeh et al., 2002; Gould et al., 1997; Malberg & Duman, 2003; Pham et al., 2003). Various types of stress induce impairments of neurogenesis. Results obtained from several studies on the stress effects on adult neurogenesis are to be presented. Thomas et al. (2007) demonstrated that acute social dominance stress inhibited cell survival but not cell proliferation. Chronic intermittent restraint stress, but not acute stress, reduced progenitor cell proliferation without affecting levels of expression in BDNF, growth associated protein-43 (GAP-43), and synaptophysin (Rosenbrock et al., 2005). In learned helplessness, an animal model of depression induced by stress, stress acutely inhibits cell proliferation regardless of the induction of learned helplessness (Heine et al., 2004). Suppression of cell proliferation and enhanced apoptosis were noticed in the dentate gyrus of pups with maternal separation, which was reversed by fluoxetine treatment (Lee et al., 2001).

Mood stabilizers are known to prevent stress-induced reduction in neurogenesis, which requires multiple target molecules involving neuroprotective and neurotrophic signaling pathways. Chronic psychosocial stress in tree shrews reduced cell proliferation in the dentate gyrus and reduced hippocampal volume that were prevented by chronic treatment with an antidepressant, tianeptine (Czeh et al., 2001). Chronic mild stress (chronic mild stress) resulted in decrease in cell proliferation and differentiation, which was paralleled by depression-like behavior in forced swim test in rats. This chronic mild stress-induced decrease in neurogenesis was prevented by chronic lithium treatment. In addition, this effect was mediated at least through inhibition of glycogen synthase kinase-3 β by lithium (Silva et al., 2008).

Chronic restraint stress induced suppression of cell proliferation which was accompanied by decreased expression of BDNF in the hippocampus (H. Xu et al., 2006). Boku et al. (2011) demonstrated that lithium and valproate, but not carbamazepine and lamotrigine, prevented the decrease in dentate gyrus-derived neural precursor cell proliferation induced by dexamethasone. However, all four mood stabilizers blocked apoptosis of dentate gyrus-derived neural precursor cells. This suggests that effects of mood stabilizers on adult neurogenesis in the dentate gyrus contribute to their therapeutic actions. This group also

showed that lithium reversed glucocorticoids-induced decrease in cell proliferation using dentate gyrus-derived neural precursor cells (Boku et al., 2010).

Interestingly, a study showed that treatment with valproate reduced cell proliferation in the subgranular zone of the dentate gyrus within the hippocampus, which was linked to significant impairment in their ability to perform a hippocampal-dependent spatial memory test. Contrary to expectation, valproate treatment caused a significant reduction in BDNF (Umka et al., 2010). But this study did not examine effects of valproate on neurogenesis under the stressed condition.

Stress-induced reduction in neurogenesis is also associated with reduction in vascular endothelial growth factor. Both angiogenesis and neurogenesis can be modulated by similar stimuli (Fabel et al., 2003). Vascular endothelial growth factor (VEGF) also has neurogenic effect (During & Cao, 2006; Silva et al., 2007). Chronic stress induces reduction in VEGF expression in the hippocampus (Heine et al., 2005; Silva et al., 2007) with concomitant reduction in proliferating cells (Heine et al., 2005). On the other hand, lithium treatment attenuated stress-induced reduction in VEGF expression and prevented stress-induced upregulation of GSK-3 β and stress-induced β -catenin. These results suggest that protection by lithium against stress-induced impairment of neurogenesis can be mediated through the GSK-3 β / β -catenin/VEGF signaling pathway (Silva et al., 2007).

Early life stress causes decrease and increase in cell proliferation and apoptosis respectively. Rat pups with maternal separation stress showed decreased cell proliferation and increased apoptosis, which was attenuated by concomitant fluoxetine treatment (Lee et al., 2001). In line with this, a study showed that early life stress effects could be counteracted by lithium treatment. Maternal deprivation induced stress decreased neuropeptide Y-like immunoreactivity in the hippocampus and striatum and increased neuropeptide Y-like immunoreactivity and corticotrophin releasing hormone-like immunoreactivity in the hypothalamus. Lithium treatment counteracted maternal deprivation effects by increasing neuropeptide Y-like immunoreactivity in the hippocampus and striatum and decreasing corticotrophin releasing hormone-like immunoreactivity in the hypothalamus (Husum & Mathe, 2002).

In addition to their preventive effect of lithium against stress-induced impairment of neurogenesis, lithium and valproate by themselves increase neurogenesis in the dentate gyrus of adult animals (G. Chen et al., 2000; Hao et al., 2004; Son et al., 2003). Neurogenesis promoting effect of lithium and valproate is ascribed to their capability to activate extracellular signal regulated kinase (ERK) signaling cascade (G. Chen et al., 2000; Hao et al., 2004).

4. The effect of mood stabilizers on stress-induced impairments in synaptic plasticity

Induction of hippocampal long term synaptic plasticity is profoundly affected by stress (Yang et al., 2004). It is well known that mild and transient stress enhances hippocampal-dependent learning and memory (Luine et al., 1996). However, exposure to more prolonged stress or severe stress definitely impairs hippocampal-dependent cognition (Sapolsky, 2003). Hippocampal-dependent learning and memory is also disrupted following chronic exposure to GCs or exposure to high dose of GCs (Joels, 2001). Stress-induced impairment of LTP is

considered to contribute to impaired hippocampal-dependent memory. Rats exposed to inescapable stress shows impairment in hippocampal-dependent memory and LTP and this impairment is mimicked by NMDA antagonist, (2R)-amino-5-phosphonovalenic acid (APV), injection into the dorsal hippocampus (Baker & Kim, 2002). Thus, the relationship between hippocampal-dependent cognitive performance and level of stress or GCs takes the inverted U pattern. Stress or GCs disrupts LTP in the various hippocampal subfields (Diamond & Park, 2000; Foy et al., 1987; Shors & Dryver, 1994; Shors et al., 1989). But similar stress paradigms resulting in impairment of LTP enhance long term depression (LTD) (L. Xu et al., 1997).

Inverted U pattern can also be applied to LTP, i.e. milder level of exposure to stress or GCs enhances LTP while more severe level of exposure to stress or GCs impairs LTP (Diamond et al., 1992; Pavlides et al., 1994). The mechanism underlying this inverted U pattern is ascribed to differential occupancy of mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). Under mild stress or low GCs condition, heavy occupancy or saturation of MR by GCs is believed to be responsible to enhancement of cognition and LTP (Sapolsky, 2003). Previous studies showed that MR occupancy enhances LTP (Pavlides et al., 1995; Vaher et al., 1994) and hippocampal-dependent spatial memory tasks (Oitzl et al., 1998).

The mechanism of LTP will be briefly described according the review by Pittenger and Duman (2008). Local elevation of cAMP and Ca^{2+} induces short term synaptic plasticity, i.e. early LTP. Ca^{2+} influx through NMDA receptors or voltage gated calcium channel activates Ca^{2+} /calmodulin dependent kinases (CaMK). Among them, Ca^{2+} /calmodulin dependent kinase II (CaMK II) is critical for early LTP. CaMK II and other CaMK phosphorylate the GluR 1 subunit of AMPA receptors, which renders AMPA receptors on the postsynaptic membrane potentiated in function. In addition, phosphorylation of AMPA receptors promotes insertion of AMPA receptors on the postsynaptic membrane. Once activated by local increase in Ca^{2+} , CaMK II phosphorylates itself persistently even after fall in local Ca^{2+} level. Thus, this property of CaMK II makes CaMK II a suitable molecule for short term synaptic change. However, long term synaptic change requires other signaling pathways: cAMP-dependent protein kinase (PKA) and mitogen-activated protein kinase (MAPK) pathways. Stimulation of PKA and MAPK pathways results in activation of regulated transcription factors which induce new genes for late LTP (L-LTP). CaMK IV is also an important molecule for L-LTP which activates regulated transcription factors like CREB.

Stress-induced synaptic plasticity seems to result at least from activation of ERK1/2 pathway by stress (Yang et al., 2004). Yang et al. (2004) showed that stress-induced suppression of LTP and enhancement of LTD in the CA1 was blocked by pretreatment with GR antagonist, 11β , 17β -11[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-estra-4-9-dien-3-one. Further, this stress effect in LTP and LTD was blocked by specific inhibitors of MEK1/2, protein kinase C, tyrosine kinase, and BDNF antisense oligonucleotides, suggesting the involvement of corticosterone-induced sustained activation of ERK1/2-coupled signaling cascades in the stress effect on LTP and LTD.

CREB is also involved in the regulation of numerous types of synaptic changes in the hippocampus, amygdala, and cortex. Since stress and mood stabilizers are known to regulate these signaling pathways involved in the mediation of LTP, it is conceivable that stress-induced synaptic alterations can be remedied by the treatment with mood stabilizers. There is substantial evidence supporting this notion.

Lithium by itself facilitates LTP in hippocampal subregions. Chronic treatment with lithium (28 days) (Nocjar et al., 2007) and subchronic treatment with lithium (14 days) enhanced LTP in the CA1 and in the dentate gyrus (Shim et al., 2007), respectively. Lithium is believed to regulate signaling cascades mediating the induction of LTP (Shim et al., 2007). Son et al. (2003) showed that acute and chronic lithium treatment enhanced LTP in the dentate gyrus of the rat. They argued that LTP enhancing effect of lithium was mediated through upregulation of signaling molecules like BDNF, phosphorylated MAPK, phosphorylated CREB, CaMK II, phosphorylated Elk, and TrkB, but not through increased neurogenesis. Silva et al. (2008) showed that lithium prevented chronic mild stress-induced upregulation GSK-3 β and downregulation of its downstream molecules bcl-2 associated athanogenes-1 and synapsin-I. Lithium also blocked depressive-like behavior resulting from chronic mild stress via inhibition of GSK-3 β . A study showed that acute immobilization stress impaired LTP induction in the CA1 region, which was restored by addition of lithium of therapeutic concentration to artificial CSF in brain slices. However, the addition of lithium to slices from non-stressed animals had no effect (Lim et al., 2005).

5. The protective effect of mood stabilizers against stress-induced apoptosis and molecular changes

As mentioned above, exposure to stress results in increase in proapoptotic molecules and decrease in antiapoptotic molecules in laboratory animals (for review, see Kubera et al., 2011). On the other hand chronic stress reduces the expression of cell surviving molecules such as bcl-2 family antiapoptotic proteins, bcl-2 and BAG-1, brain derived neurotrophic factor (BDNF), and vascular growth factor (VGF) (Nair et al., 2007; Thomas et al., 2007). It is well known that primary mood stabilizers, lithium and valproate, increase antiapoptotic proteins of bcl-2 family such as bcl-2 and bcl-xl. In addition, chronic stress activates proinflammatory cytokines and induces neuroinflammatory changes (Kubera et al., 2011). Increased apoptosis following chronic stress was observed in the hippocampal subregions and entorhinal cortex of the tree shrew (Lucassen et al., 2001).

Several previous studies suggest that mood stabilizers protect or counteract these stress-induced apoptosis or molecular changes. Bachis et al. (2008) demonstrated that chronic unpredictable mild stress for five weeks promoted neuronal apoptosis by demonstrating increased caspase-3 positive neurons in the rat cortex. This effect was reversed by treatment with desipramine. Given the fact that the most prominent mood stabilizers, lithium and valproate upregulate anti-apoptotic proteins like bcl-2 (G. Chen et al., 1999; R.W. Chen & Chuang, 1999) and suppress proapoptotic proteins, p53 and Bax (R.W. Chen & Chuang, 1999) and other anticonvulsant mood stabilizers share this neuroprotective property (X. Li et al., 2002), it is conceivable that mood stabilizers protect against stress-induced apoptosis or molecular changes.

Actually, several lines of evidence support this notion. Miller and Mathé (1997) reported that chronic lithium treatment attenuated c-fos mRNA induction by acute injection stress in the rat frontal cortex and hippocampus. The same group reported that chronic lithium treatment attenuated AP-1 DNA binding induction by acute restraint stress in the frontal cortex and hippocampus and CREB binding in the frontal cortex (Miller et al., 2007). In line with these findings, chronic stress-induced increase in CREB phosphorylation and CREB

transcriptional activity was reversed with concomitant chronic lithium treatment (Boer et al., 2008) and imipramine treatment (Boer et al., 2007).

Kosten et al. (2008) demonstrated that chronic stress reduced the expression of antiapoptotic protein genes (bcl-2 and bcl-xl) in the limbic brain, which was prevented by the treatment with different classes of antidepressant. They also showed that a major proapoptotic protein, Bax gene expression was repressed by fluoxetine. Lithium is also known to block chronic mild stress-induced depressive-like behavior. This blockade of depressive-like behavior is accompanied by prevention of mild stress-induced increase of GSK-3 β and decrease in its downstream targets, BAG-1, and synapsin- I (Silva et al., 2008). This finding suggests that neuroprotective action of lithium against chronic stress effect involves the suppression of GSK-3 β .

6. Stress-induced neuroinflammatory reactions are likely to be prevented by mood stabilizers

Exposure to psychosocial stressors leads to increased proinflammatory molecules as well as behavioral or mood disturbances in humans and animals. Stress-induced depressive-like behavior is associated with increase in interleukin 1- β (IL-1 β), tumor necrosis factor- α (TNF- α), IL-6, nuclear factor κ B (NF κ B), cyclooxygenase-2(COX-2), expression of Toll-like receptors and lipid peroxidation in animals (Kubera et al., 2011). In humans, various chronic psychosocial stressors like burnout, low socioeconomic status, childhood adversity and maltreatment, and loneliness also affect adversely stress response and induce increase in proinflammatory molecules (Hansel et al., 2010). Increased level of proinflammatory cytokines was observed in patients with stress-related disorders like depression (Maes, 1995) and posttraumatic stress disorder (Hoge et al., 2009). Depressed and manic states in bipolar disorder are considered to be a proinflammatory state. A study about cytokine levels in euthymic bipolar patients suggested that proinflammatory state resolved in euthymic state (Guloksuz et al., 2010). On the other hand, antidepressant therapy decreases proinflammatory cytokines, IL- β , IL-6, and TNF- α (Kubera et al., 2011). This line of studies suggests that pathophysiology of bipolar disorder and stress effects share the mechanism leading to proinflammatory state.

Chronic stress-induced increase in proinflammatory cytokines is associated with anhedonia (decreased sucrose intake) in laboratory animals (Grippe et al., 2005). Decrease in hippocampal IL-1 was observed following chronic stress and only chronic IL-1 injection caused the similar behaviors which were observed in animals exposed to chronic stress (Goshen & Yirmiya, 2009). There is evidence to support that IL-1 β is a mediator of stress-induced behaviors (Badowska-Szalewska et al., 2009). A study suggested IL-1 β activity is coupled to phospholipase A₂ (PLA₂) by showing inhibition of IL-1 β activity with nonspecific PLA₂ antagonist, quinacrine (Song et al., 2007). Besides, IL- β , TNF- α and NF κ B increase in the brain after chronic stress (Grippe et al., 2005; Gu et al., 2009; Madrigal et al., 2002; Madrigal et al., 2001). NF κ B recognizes specific DNA sequences in the promoters of genes encoding proinflammatory factors including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase(iNOS) (Kubera et al., 2011). Stress also increases reactive oxygen species and iNOS (Madrigal et al., 2001; Olivenza et al., 2000).

On the other hand, it is known that chronic treatment with lithium, carbamazepine, and valproate at therapeutically relevant doses decrease arachidonic acid turnover and the level of COX-2 and prostaglandin E₂ (PGE₂) in the rat brain (Chang et al., 1996; Rao et al., 2008). Lithium and carbamazepine reduce the AP-2 binding activity, which leads to decreased transcription, translation and activity of arachidonic acid-specific and calcium dependent phospholipase A₂ (cPLA₂) (Bosetti et al., 2003; Rao et al., 2008), a PLA₂ isoform specific for release of arachidonic acid from membrane phospholipids of the brain, whereas valproate inhibits long chain acyl-CoA synthetase and thus decreases the arachidonic acid turnover (Rao et al., 2008). However, chronic treatment with lithium does not affect COX-1 or Ca²⁺-independent PLA₂ (Bosetti et al., 2002). Chronic treatment with valproate also decreases DNA binding activity of NFκB in the rat frontal cortex (Rao et al., 2007a). Chronic administration of lamotrigine, an effective mood stabilizer blocking the relapse of depressive episode, decreases the level of COX-2 protein and mRNA expression in the rat frontal cortex without affecting the protein level of PLA₂ (Lee et al., 2008).

In addition, decreased turnover by chronic treatment with mood stabilizers is associated with increased expression of bcl-2 and BDNF in the brain. Chronic deprivation of dietary essential n-3 polyunsaturated fatty acids results in bipolar disorder-like symptoms in rats (DeMar et al., 2006) and increased expression of cPLA₂ and COX-2 (DeMar et al., 2006; Rao et al., 2007b). Deprivation of essential n-3 polyunsaturated fatty acids also leads to decreased expression of phosphorylated CREB and BDNF mRNA and proteins (Rao et al., 2007c).

7. Mood stabilizers attenuate stress-induced oxidative stress

Chronic stress increases the level of oxidative stress. Lucca et al. (2009) reported that chronic stress increased thiobarbituric acid reactive substances (TBARS) in the brain, a parameter of increased oxidative stress. In line with this study, lithium and valproate reversed amphetamine treatment-induced elevation of TBARS and prevented hyperactivity in an animal model of mania (Frey et al., 2006). These studies suggest that mood stabilizers, lithium and valproate, share the capability to prevent stress-induced increase in oxidative stress and that this anti-oxidant effect may contribute to their therapeutic actions. Lithium and valproate at therapeutically relevant concentrations in humans inhibited glutamate-induced increase in intracellular free Ca²⁺ concentration, lipid peroxidation, and protein oxidation in cultured rat cerebral cortical cells, which suggests that lithium and valproate inhibit glutamate-induced excitotoxicity by inhibiting oxidative stress (Shao et al., 2005).

8. Are mood stabilizers efficacious for treating traumatic stress-related disorders?

Experiences can modify gene functions without DNA sequence changes and these mechanisms are called epigenetic modification. Epigenetic modification encompasses DNA methylation and histone acetylation and methylation (Krishnan & Nestler, 2008). Deprivation of maternal care in rat pups resulted in increased methylation of promoter region of GR gene in the hippocampus (Tsankova et al., 2007), and thus repressed gene expression. Early maltreatment also led to lasting increased methylation and decreased expression of BDNF gene in the prefrontal cortex of adult rats (Roth et al., 2009). A human study reported the association of higher level of methylation in serotonin transporter promoter with increased

risk to unresolved loss or other trauma among adoptees (van et al., 2010). In an animal model of posttraumatic stress disorder (PTSD), traumatized rats showed hypermethylation of BDNF gene in the dorsal CA1 with reduced expression of BDNF mRNA. However, decreased methylation of BDNF gene was observed in the CA3, which suggests region-specificity (Roth et al., 2011). Epigenetic modification is involved in stress-related disorders like depression, bipolar disorder, and PTSD (Mill & Petronis, 2007; Petronis, 2003). On the other hand, among mood stabilizers, valproate is a histone deacetylase (HDAC) inhibitor and HDAC is a direct target of valproate (Phiel & Klein, 2001). Neuroprotective action of valproate is associated with hyperacetylation of histone (Chuang, 2005). Valproate was found to produce DNA demethylation and hyperacetylation in glutamate transporter-1 gene promoter in cultured primary astrocytes (Perisic et al., 2010).

Fig. 1. Schematic representation of stress induced neural changes antistress effects of mood stabilizers. Abbreviations used: Bcl-2: B-cell leukemia/lymphoma-2; BDNF: brain-derived neurotrophic factor; VEGF: vascular endothelial growth factor; Bax: bcl-2-associated X protein; BAD: bcl-associated death protein; ROS: reactive oxygen species; PFC: prefrontal cortex; LTP: long-term potentiation; LTD: long-term depression; IL-1,6: interleukin-1,6; TNF- α : tumor necrosis factor- α ; cPLA₂: cytosolic phospholipase A₂; COX-1,2: cyclooxygenase-1,2; NF κ B: nuclear transcription factor kappa B; AA: arachidonic acid

Taken together, it is suggested that mood stabilizers, especially valproate might be efficacious for treating traumatic stress-related disorders like PTSD. A systemic review suggest that valproate can be effective for the treatment of PTSD by reducing hyperarousal, improving irritability, anger outburst, and mood although it remains that more double blind studies are needed (Adamou et al., 2007). Lamotrigine significantly suppressed stress responses to public speech including suppression of stress hormones such as growth hormones and cortisol (Makatsori et al., 2004).

9. Conclusion

We live in a world full of stress. Inescapable changes in our life styles are imposing tremendous stress on us. Stress profoundly affects morphology and functions of the brain which is the central organ mediating stress response (McEwen, 2004). In the mental health area, we are increasingly faced with heavy burden of stress-related mental disorders like depression and bipolar disorder. Even though bipolar disorder is a serious mental disorder, pharmacological treatment of bipolar disorder is not always satisfactory. Pathophysiology of bipolar disorder and the mechanism of therapeutic actions of mood stabilizers remain to be elucidated.

Stress effects on the brain i.e. altered structural plasticity, impaired neurogenesis, altered synaptic efficacy, accelerated apoptosis, cognitive impairment, and proclivity to neuroinflammation are mediated through overlapping cascades and molecules involved in cell survival and death. For example, exposure to chronic mild stress in mice produces cognitive impairment accompanied by increased proinflammatory cytokines and stress hormones, decreased BDNF, and enhanced cell damage (S. Li et al., 2008). Furthermore, mood stabilizers have capabilities to reverse stress-induced behavioral impairments. Chronic stress-induced spatial memory impairment is attenuated by chronic lithium treatment (Vasconcellos et al., 2003). Chronic or subchronic treatment with lamotrigine ameliorates behavioral parameters in stress-induced animal models of depression with concomitant restoration of stress-induced downregulation of neuroprotective proteins (N. Li et al., 2010; N. Li et al., 2011). Interestingly, protective effects against stress-induced deleterious effects on the brain (anti-stress effects) seem to be shared by most mood stabilizers. As described in the preceding sections, effects of stress are mediated through signaling cascades that are also the targets of mood stabilizers. In this context, mood stabilizing effects may be ascribed to anti-stress effects of mood stabilizers.

10. Acknowledgment

The authors would like to thank Dr. Jeewon Lee and Dr. Hye-won Baek for their contribution to the revision process of this article.

11. References

- Adamou, M., Puchalska, S., Plummer, W. & Hale, A. S. (2007). Valproate in the Treatment of Ptsd: Systematic Review and Meta Analysis. *Curr Med Res Opin*, Vol.23, No.6, (Jun, 2007), pp. (1285-1291), ISSN. 1473-4877 (Electronic)

- Bachis, A., Cruz, M. I., Nosheny, R. L. & Mocchetti, I. (2008). Chronic Unpredictable Stress Promotes Neuronal Apoptosis in the Cerebral Cortex. *Neurosci Lett*, Vol.442, No.2, (Sep 12, 2008), pp. (104-108), ISSN. 0304-3940 (Print)
- Bachmann, R. F., Schloesser, R. J., Gould, T. D. & Manji, H. K. (2005). Mood Stabilizers Target Cellular Plasticity and Resilience Cascades: Implications for the Development of Novel Therapeutics. *Mol Neurobiol*, Vol.32, No.2, (Oct, 2005), pp. (173-202), ISSN. 0893-7648 (Print)
- Badowska-Szalewska, E., Klejbor, I., Sidor-Kaczmarek, J., Cecot, T., Lietzau, G., Spodnik, J. H. & Morys, J. (2009). Stress-Induced Changes of Interleukin-1beta within the Limbic System in the Rat. *Folia Morphol (Warsz)*, Vol.68, No.3, (Aug, 2009), pp. (119-128), ISSN. 0015-5659 (Print)
- Baker, K. B. & Kim, J. J. (2002). Effects of Stress and Hippocampal Nmda Receptor Antagonism on Recognition Memory in Rats. *Learn Mem*, Vol.9, No.2, (Mar-Apr, 2002), pp. (58-65), ISSN. 1072-0502 (Print)
- Baldessarini, R. J., Tondo, L. & Hennen, J. (1999). Effects of Lithium Treatment and Its Discontinuation on Suicidal Behavior in Bipolar Manic-Depressive Disorders. *J Clin Psychiatry*, Vol.60 Suppl 2, 1999, pp. (77-84; discussion 111-116), ISSN. 0160-6689 (Print)
- Belmaker, R. H. (2004). Bipolar Disorder. *N Engl J Med*, Vol.351, No.5, (Jul 29, 2004), pp. (476-486), ISSN. 1533-4406 (Electronic)
- Biebl, M., Cooper, C. M., Winkler, J. & Kuhn, H. G. (2000). Analysis of Neurogenesis and Programmed Cell Death Reveals a Self-Renewing Capacity in the Adult Rat Brain. *Neurosci Lett*, Vol.291, No.1, (Sep 8, 2000), pp. (17-20), ISSN. 0304-3940 (Print)
- Blendy, J. A. (2006). The Role of Creb in Depression and Antidepressant Treatment. *Biol Psychiatry*, Vol.59, No.12, (Jun 15, 2006), pp. (1144-1150), ISSN. 0006-3223 (Print)
- Bloss, E. B., Janssen, W. G., Ohm, D. T., Yuk, F. J., Wadsworth, S., Saardi, K. M., McEwen, B. S. & Morrison, J. H. (2011). Evidence for Reduced Experience-Dependent Dendritic Spine Plasticity in the Aging Prefrontal Cortex. *J Neurosci*, Vol.31, No.21, (May 25, 2011), pp. (7831-7839), ISSN. 1529-2401 (Electronic)
- Boer, U., Alejel, T., Beimesche, S., Cierny, I., Krause, D., Knepel, W. & Flugge, G. (2007). Cre/Creb-Driven up-Regulation of Gene Expression by Chronic Social Stress in Cre-Luciferase Transgenic Mice: Reversal by Antidepressant Treatment. *PLoS One*, Vol.2, No.5, 2007, pp. (e431), ISSN. 1932-6203 (Electronic)
- Boer, U., Cierny, I., Krause, D., Heinrich, A., Lin, H., Mayr, G., Hiemke, C. & Knepel, W. (2008). Chronic Lithium Salt Treatment Reduces Cre/Creb-Directed Gene Transcription and Reverses Its Upregulation by Chronic Psychosocial Stress in Transgenic Reporter Gene Mice. *Neuropsychopharmacology*, Vol.33, No.10, (Sep, 2008), pp. (2407-2415), ISSN. 1740-634X (Electronic)
- Boku, S., Nakagawa, S. & Koyama, T. (2010). Glucocorticoids and Lithium in Adult Hippocampal Neurogenesis. *Vitam Horm*, Vol.82, 2010, pp. (421-431), ISSN. 0083-6729 (Print)
- Boku, S., Nakagawa, S., Masuda, T., Nishikawa, H., Kato, A., Toda, H., Song, N., Kitaichi, Y., Inoue, T. & Koyama, T. (2011). Effects of Mood Stabilizers on Adult Dentate Gyrus-Derived Neural Precursor Cells. *Prog Neuropsychopharmacol Biol Psychiatry*, Vol.35, No.1, (Jan 15, 2011), pp. (111-117), ISSN. 1878-4216 (Electronic)

- Bosetti, F., Rintala, J., Seemann, R., Rosenberger, T. A., Contreras, M. A., Rapoport, S. I. & Chang, M. C. (2002). Chronic Lithium Downregulates Cyclooxygenase-2 Activity and Prostaglandin E(2) Concentration in Rat Brain. *Mol Psychiatry*, Vol.7, No.8, 2002), pp. (845-850), ISSN. 1359-4184 (Print)
- Bosetti, F., Weerasinghe, G. R., Rosenberger, T. A. & Rapoport, S. I. (2003). Valproic Acid Down-Regulates the Conversion of Arachidonic Acid to Eicosanoids Via Cyclooxygenase-1 and -2 in Rat Brain. *J Neurochem*, Vol.85, No.3, (May, 2003), pp. (690-696), ISSN. 0022-3042 (Print)
- Bourin, M., Chenu, F. & Hascoet, M. (2009). The Role of Sodium Channels in the Mechanism of Action of Antidepressants and Mood Stabilizers. *Curr Drug Targets*, Vol.10, No.11, (Nov, 2009), pp. (1052-1060), ISSN. 1873-5592 (Electronic)
- Brown, E. S., Zaidel, L., Allen, G., McColl, R., Vazquez, M. & Ringe, W. K. (2010). Effects of Lamotrigine on Hippocampal Activation in Corticosteroid-Treated Patients. *J Affect Disord*, Vol.126, No.3, (Nov, 2010), pp. (415-419), ISSN. 1573-2517 (Electronic)
- Brown, J., Cooper-Kuhn, C. M., Kempermann, G., Van Praag, H., Winkler, J., Gage, F. H. & Kuhn, H. G. (2003). Enriched Environment and Physical Activity Stimulate Hippocampal but Not Olfactory Bulb Neurogenesis. *Eur J Neurosci*, Vol.17, No.10, (May, 2003), pp. (2042-2046), ISSN. 0953-816X (Print)
- Brunson, K. L., Chen, Y., Avishai-Eliner, S. & Baram, T. Z. (2003). Stress and the Developing Hippocampus: A Double-Edged Sword? *Mol Neurobiol*, Vol.27, No.2, (Apr, 2003), pp. (121-136), ISSN. 0893-7648 (Print)
- Buwalda, B., Kole, M. H., Veenema, A. H., Huininga, M., de Boer, S. F., Korte, S. M. & Koolhaas, J. M. (2005). Long-Term Effects of Social Stress on Brain and Behavior: A Focus on Hippocampal Functioning. *Neurosci Biobehav Rev*, Vol.29, No.1, (Feb, 2005), pp. (83-97), ISSN. 0149-7634 (Print)
- Cade, J. F. (1949). Lithium Salts in the Treatment of Psychotic Excitement. *Med J Aust*, Vol.2, No.10, (Sep 3, 1949), pp. (349-352), ISSN. 0025-729X (Print)
- Cameron, H. A. & McKay, R. D. (2001). Adult Neurogenesis Produces a Large Pool of New Granule Cells in the Dentate Gyrus. *J Comp Neurol*, Vol.435, No.4, (Jul 9, 2001), pp. (406-417), ISSN. 0021-9967 (Print)
- Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A. & Poulton, R. (2003). Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science*, Vol.301, No.5631, (Jul 18, 2003), pp. (386-389), ISSN. 1095-9203 (Electronic)
- Chang, M. C., Grange, E., Rabin, O., Bell, J. M., Allen, D. D. & Rapoport, S. I. (1996). Lithium Decreases Turnover of Arachidonate in Several Brain Phospholipids. *Neurosci Lett*, Vol.220, No.3, (Dec 20, 1996), pp. (171-174), ISSN. 0304-3940 (Print)
- Chen, G., Rajkowska, G., Du, F., Seraji-Bozorgzad, N. & Manji, H. K. (2000). Enhancement of Hippocampal Neurogenesis by Lithium. *J Neurochem*, Vol.75, No.4, (Oct, 2000), pp. (1729-1734), ISSN. 0022-3042 (Print)
- Chen, G., Zeng, W. Z., Yuan, P. X., Huang, L. D., Jiang, Y. M., Zhao, Z. H. & Manji, H. K. (1999). The Mood-Stabilizing Agents Lithium and Valproate Robustly Increase the Levels of the Neuroprotective Protein Bcl-2 in the Cns. *J Neurochem*, Vol.72, No.2, (Feb, 1999), pp. (879-882), ISSN. 0022-3042 (Print)
- Chen, R. W. & Chuang, D. M. (1999). Long Term Lithium Treatment Suppresses P53 and Bax Expression but Increases Bcl-2 Expression. A Prominent Role in Neuroprotection

- against Excitotoxicity. *J Biol Chem*, Vol.274, No.10, (Mar 5, 1999), pp. (6039-6042), ISSN. 0021-9258 (Print)
- Chuang, D. M. (2005). The Antiapoptotic Actions of Mood Stabilizers: Molecular Mechanisms and Therapeutic Potentials. *Ann N Y Acad Sci*, Vol.1053, (Aug, 2005), pp. (195-204), ISSN. 0077-8923 (Print)
- Cook, S. C.&Wellman, C. L. (2004). Chronic Stress Alters Dendritic Morphology in Rat Medial Prefrontal Cortex. *J Neurobiol*, Vol.60, No.2, (Aug, 2004), pp. (236-248), ISSN. 0022-3034 (Print)
- Czeh, B., Michaelis, T., Watanabe, T., Frahm, J., de Biurrun, G., van Kampen, M., Bartolomucci, A.&Fuchs, E. (2001). Stress-Induced Changes in Cerebral Metabolites, Hippocampal Volume, and Cell Proliferation Are Prevented by Antidepressant Treatment with Tianeptine. *Proc Natl Acad Sci U S A*, Vol.98, No.22, (Oct 23, 2001), pp. (12796-12801), ISSN. 0027-8424 (Print)
- Czeh, B., Welt, T., Fischer, A. K., Erhardt, A., Schmitt, W., Muller, M. B., Toschi, N., Fuchs, E.&Keck, M. E. (2002). Chronic Psychosocial Stress and Concomitant Repetitive Transcranial Magnetic Stimulation: Effects on Stress Hormone Levels and Adult Hippocampal Neurogenesis. *Biol Psychiatry*, Vol.52, No.11, (Dec 1, 2002), pp. (1057-1065), ISSN. 0006-3223 (Print)
- Dayer, A. G., Cleaver, K. M., Abouantoun, T.&Cameron, H. A. (2005). New Gabaergic Interneurons in the Adult Neocortex and Striatum Are Generated from Different Precursors. *J Cell Biol*, Vol.168, No.3, (Jan 31, 2005), pp. (415-427), ISSN. 0021-9525 (Print)
- de Quervain, D. J., Roozendaal, B.&McGaugh, J. L. (1998). Stress and Glucocorticoids Impair Retrieval of Long-Term Spatial Memory. *Nature*, Vol.394, No.6695, (Aug 20, 1998), pp. (787-790), ISSN. 0028-0836 (Print)
- DeCarolis, N. A.&Eisch, A. J. (2010). Hippocampal Neurogenesis as a Target for the Treatment of Mental Illness: A Critical Evaluation. *Neuropharmacology*, Vol.58, No.6, (May, 2010), pp. (884-893), ISSN. 1873-7064 (Electronic)
- DeMar, J. C., Jr., Ma, K., Bell, J. M., Igarashi, M., Greenstein, D.&Rapoport, S. I. (2006). One Generation of N-3 Polyunsaturated Fatty Acid Deprivation Increases Depression and Aggression Test Scores in Rats. *J Lipid Res*, Vol.47, No.1, (Jan, 2006), pp. (172-180), ISSN. 0022-2275 (Print)
- Diamond, D. M., Bennett, M. C., Fleshner, M.&Rose, G. M. (1992). Inverted-U Relationship between the Level of Peripheral Corticosterone and the Magnitude of Hippocampal Primed Burst Potentiation. *Hippocampus*, Vol.2, No.4, (Oct, 1992), pp. (421-430), ISSN. 1050-9631 (Print)
- Diamond, D. M.&Park, C. R. (2000). Predator Exposure Produces Retrograde Amnesia and Blocks Synaptic Plasticity. Progress toward Understanding How the Hippocampus Is Affected by Stress. *Ann N Y Acad Sci*, Vol.911, (Jun, 2000), pp. (453-455), ISSN. 0077-8923 (Print)
- Dixon, J. F.&Hokin, L. E. (1998). Lithium Acutely Inhibits and Chronically up-Regulates and Stabilizes Glutamate Uptake by Presynaptic Nerve Endings in Mouse Cerebral Cortex. *Proc Natl Acad Sci U S A*, Vol.95, No.14, (Jul 7, 1998), pp. (8363-8368), ISSN. 0027-8424 (Print)
- Drevets, W. C. (2003). Neuroimaging Abnormalities in the Amygdala in Mood Disorders. *Ann N Y Acad Sci*, Vol.985, (Apr, 2003), pp. (420-444), ISSN. 0077-8923 (Print)

- Drevets, W. C., Price, J. L., Simpson, J. R., Jr., Todd, R. D., Reich, T., Vannier, M. & Raichle, M. E. (1997). Subgenual Prefrontal Cortex Abnormalities in Mood Disorders. *Nature*, Vol.386, No.6627, (Apr 24, 1997), pp. (824-827), ISSN. 0028-0836 (Print)
- Duman, R. S., Malberg, J. & Thome, J. (1999). Neural Plasticity to Stress and Antidepressant Treatment. *Biol Psychiatry*, Vol.46, No.9, (Nov 1, 1999), pp. (1181-1191), ISSN. 0006-3223 (Print)
- During, M. J. & Cao, L. (2006). Vegf, a Mediator of the Effect of Experience on Hippocampal Neurogenesis. *Curr Alzheimer Res*, Vol.3, No.1, (Feb, 2006), pp. (29-33), ISSN. 1567-2050 (Print)
- Eriksson, P. S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A. M., Nordborg, C., Peterson, D. A. & Gage, F. H. (1998). Neurogenesis in the Adult Human Hippocampus. *Nat Med*, Vol.4, No.11, (Nov, 1998), pp. (1313-1317), ISSN. 1078-8956 (Print)
- Fabel, K., Tam, B., Kaufer, D., Baiker, A., Simmons, N., Kuo, C. J. & Palmer, T. D. (2003). Vegf Is Necessary for Exercise-Induced Adult Hippocampal Neurogenesis. *Eur J Neurosci*, Vol.18, No.10, (Nov, 2003), pp. (2803-2812), ISSN. 0953-816X (Print)
- Fontella, F. U., Vendite, D. A., Tabajara, A. S., Porciuncula, L. O., da Silva Torres, I. L., Jardim, F. M., Martini, L., Souza, D. O., Netto, C. A. & Dalmaz, C. (2004). Repeated Restraint Stress Alters Hippocampal Glutamate Uptake and Release in the Rat. *Neurochem Res*, Vol.29, No.9, (Sep, 2004), pp. (1703-1709), ISSN. 0364-3190 (Print)
- Foy, M. R., Stanton, M. E., Levine, S. & Thompson, R. F. (1987). Behavioral Stress Impairs Long-Term Potentiation in Rodent Hippocampus. *Behav Neural Biol*, Vol.48, No.1, (Jul, 1987), pp. (138-149), ISSN. 0163-1047 (Print)
- Frey, B. N., Valvassori, S. S., Reus, G. Z., Martins, M. R., Petronilho, F. C., Bardini, K., Dal-Pizzol, F., Kapczinski, F. & Quevedo, J. (2006). Changes in Antioxidant Defense Enzymes after D-Amphetamine Exposure: Implications as an Animal Model of Mania. *Neurochem Res*, Vol.31, No.5, (May, 2006), pp. (699-703), ISSN. 0364-3190 (Print)
- Garrett, A. & Chang, K. (2008). The Role of the Amygdala in Bipolar Disorder Development. *Dev Psychopathol*, Vol.20, No.4, (Fall, 2008), pp. (1285-1296), ISSN. 1469-2198 (Electronic)
- Goshen, I. & Yirmiya, R. (2009). Interleukin-1 (Il-1): A Central Regulator of Stress Responses. *Front Neuroendocrinol*, Vol.30, No.1, (Jan, 2009), pp. (30-45), ISSN. 1095-6808 (Electronic)
- Gould, E., McEwen, B. S., Tanapat, P., Galea, L. A. & Fuchs, E. (1997). Neurogenesis in the Dentate Gyrus of the Adult Tree Shrew Is Regulated by Psychosocial Stress and Nmda Receptor Activation. *J Neurosci*, Vol.17, No.7, (Apr 1, 1997), pp. (2492-2498), ISSN. 0270-6474 (Print)
- Gould, E., Reeves, A. J., Graziano, M. S. & Gross, C. G. (1999). Neurogenesis in the Neocortex of Adult Primates. *Science*, Vol.286, No.5439, (Oct 15, 1999), pp. (548-552), ISSN. 0036-8075 (Print)
- Grippe, A. J., Francis, J., Beltz, T. G., Felder, R. B. & Johnson, A. K. (2005). Neuroendocrine and Cytokine Profile of Chronic Mild Stress-Induced Anhedonia. *Physiol Behav*, Vol.84, No.5, (Apr 13, 2005), pp. (697-706), ISSN. 0031-9384 (Print)
- Gu, H., Tang, C., Peng, K., Sun, H. & Yang, Y. (2009). Effects of Chronic Mild Stress on the Development of Atherosclerosis and Expression of Toll-Like Receptor 4 Signaling

- Pathway in Adolescent Apolipoprotein E Knockout Mice. *J Biomed Biotechnol*, Vol.2009, 2009), pp. (613879), ISSN. 1110-7251 (Electronic)
- Guloksuz, S., Cetin, E. A., Cetin, T., Deniz, G., Oral, E. T.&Nutt, D. J. (2010). Cytokine Levels in Euthymic Bipolar Patients. *J Affect Disord*, Vol.126, No.3, (Nov, 2010), pp. (458-462), ISSN. 1573-2517 (Electronic)
- Hammen, C. (2005). Stress and Depression. *Annu Rev Clin Psychol*, Vol.1, 2005), pp. (293-319), ISSN. 1548-5943 (Print)
- Hammen, C., Brennan, P. A.&Shih, J. H. (2004). Family Discord and Stress Predictors of Depression and Other Disorders in Adolescent Children of Depressed and Nondepressed Women. *J Am Acad Child Adolesc Psychiatry*, Vol.43, No.8, (Aug, 2004), pp. (994-1002), ISSN. 0890-8567 (Print)
- Hansel, A., Hong, S., Camara, R. J.&von Kanel, R. (2010). Inflammation as a Psychophysiological Biomarker in Chronic Psychosocial Stress. *Neurosci Biobehav Rev*, Vol.35, No.1, (Sep, 2010), pp. (115-121), ISSN. 1873-7528 (Electronic)
- Hao, Y., Creson, T., Zhang, L., Li, P., Du, F., Yuan, P., Gould, T. D., Manji, H. K.&Chen, G. (2004). Mood Stabilizer Valproate Promotes Erk Pathway-Dependent Cortical Neuronal Growth and Neurogenesis. *J Neurosci*, Vol.24, No.29, (Jul 21, 2004), pp. (6590-6599), ISSN. 1529-2401 (Electronic)
- Hashimoto, R., Hough, C., Nakazawa, T., Yamamoto, T.&Chuang, D. M. (2002). Lithium Protection against Glutamate Excitotoxicity in Rat Cerebral Cortical Neurons: Involvement of Nmda Receptor Inhibition Possibly by Decreasing Nr2b Tyrosine Phosphorylation. *J Neurochem*, Vol.80, No.4, (Feb, 2002), pp. (589-597), ISSN. 0022-3042 (Print)
- Heine, V. M., Maslam, S., Zareno, J., Joels, M.&Lucassen, P. J. (2004). Suppressed Proliferation and Apoptotic Changes in the Rat Dentate Gyrus after Acute and Chronic Stress Are Reversible. *Eur J Neurosci*, Vol.19, No.1, (Jan, 2004), pp. (131-144), ISSN. 0953-816X (Print)
- Heine, V. M., Zareno, J., Maslam, S., Joels, M.&Lucassen, P. J. (2005). Chronic Stress in the Adult Dentate Gyrus Reduces Cell Proliferation near the Vasculature and Vegf and Flk-1 Protein Expression. *Eur J Neurosci*, Vol.21, No.5, (Mar, 2005), pp. (1304-1314), ISSN. 0953-816X (Print)
- Henn, F. A.&Vollmayr, B. (2004). Neurogenesis and Depression: Etiology or Epiphenomenon? *Biol Psychiatry*, Vol.56, No.3, (Aug 1, 2004), pp. (146-150), ISSN. 0006-3223 (Print)
- Hoge, E. A., Brandstetter, K., Moshier, S., Pollack, M. H., Wong, K. K.&Simon, N. M. (2009). Broad Spectrum of Cytokine Abnormalities in Panic Disorder and Posttraumatic Stress Disorder. *Depress Anxiety*, Vol.26, No.5, 2009), pp. (447-455), ISSN. 1520-6394 (Electronic)
- Husum, H.&Mathe, A. A. (2002). Early Life Stress Changes Concentrations of Neuropeptide Y and Corticotropin-Releasing Hormone in Adult Rat Brain. Lithium Treatment Modifies These Changes. *Neuropsychopharmacology*, Vol.27, No.5, (Nov, 2002), pp. (756-764), ISSN. 0893-133X (Print)
- Joels, M. (2001). Corticosteroid Actions in the Hippocampus. *J Neuroendocrinol*, Vol.13, No.8, (Aug, 2001), pp. (657-669), ISSN. 0953-8194 (Print)

- Johnson, S. A., Wang, J. F., Sun, X., McEwen, B. S., Chattarji, S. & Young, L. T. (2009). Lithium Treatment Prevents Stress-Induced Dendritic Remodeling in the Rodent Amygdala. *Neuroscience*, Vol.163, No.1, (Sep 29, 2009), pp. (34-39), ISSN. 1873-7544 (Electronic)
- Karege, F., Schwald, M., Papadimitriou, P., Lachausse, C. & Cisse, M. (2004). The Camp-Dependent Protein Kinase a and Brain-Derived Neurotrophic Factor Expression in Lymphoblast Cells of Bipolar Affective Disorder. *J Affect Disord*, Vol.79, No.1-3, (Apr, 2004), pp. (187-192), ISSN. 0165-0327 (Print)
- Kempermann, G., Kuhn, H. G. & Gage, F. H. (1997). More Hippocampal Neurons in Adult Mice Living in an Enriched Environment. *Nature*, Vol.386, No.6624, (Apr 3, 1997), pp. (493-495), ISSN. 0028-0836 (Print)
- Kornack, D. R. & Rakic, P. (1999). Continuation of Neurogenesis in the Hippocampus of the Adult Macaque Monkey. *Proc Natl Acad Sci U S A*, Vol.96, No.10, (May 11, 1999), pp. (5768-5773), ISSN. 0027-8424 (Print)
- Kosten, T. A., Galloway, M. P., Duman, R. S., Russell, D. S. & D'Sa, C. (2008). Repeated Unpredictable Stress and Antidepressants Differentially Regulate Expression of the Bcl-2 Family of Apoptotic Genes in Rat Cortical, Hippocampal, and Limbic Brain Structures. *Neuropsychopharmacology*, Vol.33, No.7, (Jun, 2008), pp. (1545-1558), ISSN. 0893-133X (Print)
- Krishnan, V. & Nestler, E. J. (2008). The Molecular Neurobiology of Depression. *Nature*, Vol.455, No.7215, (Oct 16, 2008), pp. (894-902), ISSN. 1476-4687 (Electronic)
- Kubera, M., Obuchowicz, E., Goehler, L., Brzeszcz, J. & Maes, M. (2011). In Animal Models, Psychosocial Stress-Induced (Neuro)Inflammation, Apoptosis and Reduced Neurogenesis Are Associated to the Onset of Depression. *Prog Neuropsychopharmacol Biol Psychiatry*, Vol.35, No.3, (Apr 29, 2011), pp. (744-759), ISSN. 1878-4216 (Electronic)
- Kuhn, H. G., Biebl, M., Wilhelm, D., Li, M., Friedlander, R. M. & Winkler, J. (2005). Increased Generation of Granule Cells in Adult Bcl-2-Overexpressing Mice: A Role for Cell Death During Continued Hippocampal Neurogenesis. *Eur J Neurosci*, Vol.22, No.8, (Oct, 2005), pp. (1907-1915), ISSN. 0953-816X (Print)
- Lee, H. J., Ertley, R. N., Rapoport, S. I., Bazinet, R. P. & Rao, J. S. (2008). Chronic Administration of Lamotrigine Downregulates Cox-2 Mrna and Protein in Rat Frontal Cortex. *Neurochem Res*, Vol.33, No.5, (May, 2008), pp. (861-866), ISSN. 0364-3190 (Print)
- Lee, H. J., Kim, J. W., Yim, S. V., Kim, M. J., Kim, S. A., Kim, Y. J., Kim, C. J. & Chung, J. H. (2001). Fluoxetine Enhances Cell Proliferation and Prevents Apoptosis in Dentate Gyrus of Maternally Separated Rats. *Mol Psychiatry*, Vol.6, No.6, (Nov, 2001), pp. (610, 725-618), ISSN. 1359-4184 (Print)
- Li, N., He, X., Qi, X., Zhang, Y. & He, S. (2010). The Mood Stabilizer Lamotrigine Produces Antidepressant Behavioral Effects in Rats: Role of Brain-Derived Neurotrophic Factor. *J Psychopharmacol*, Vol.24, No.12, (Dec, 2010), pp. (1772-1778), ISSN. 1461-7285 (Electronic)
- Li, N., He, X., Zhang, Y., Qi, X., Li, H., Zhu, X. & He, S. (2011). Brain-Derived Neurotrophic Factor Signalling Mediates Antidepressant Effects of Lamotrigine. *Int J Neuropsychopharmacol*, Vol.14, No.8, (Sep, 2011), pp. (1091-1098), ISSN. 1469-5111 (Electronic)

- Li, S., Wang, C., Wang, W., Dong, H., Hou, P. & Tang, Y. (2008). Chronic Mild Stress Impairs Cognition in Mice: From Brain Homeostasis to Behavior. *Life Sci*, Vol.82, No.17-18, (Apr 23, 2008), pp. (934-942), ISSN. 0024-3205 (Print)
- Li, X., Ketter, T. A. & Frye, M. A. (2002). Synaptic, Intracellular, and Neuroprotective Mechanisms of Anticonvulsants: Are They Relevant for the Treatment and Course of Bipolar Disorders? *J Affect Disord*, Vol.69, No.1-3, (May, 2002), pp. (1-14), ISSN. 0165-0327 (Print)
- Lim, K. Y., Yang, J. J., Lee, D. S., Noh, J. S., Jung, M. W. & Chung, Y. K. (2005). Lithium Attenuates Stress-Induced Impairment of Long-Term Potentiation Induction. *Neuroreport*, Vol.16, No.14, (Sep 28, 2005), pp. (1605-1608), ISSN. 0959-4965 (Print)
- Liston, C., Miller, M. M., Goldwater, D. S., Radley, J. J., Rocher, A. B., Hof, P. R., Morrison, J. H. & McEwen, B. S. (2006). Stress-Induced Alterations in Prefrontal Cortical Dendritic Morphology Predict Selective Impairments in Perceptual Attentional Set-Shifting. *J Neurosci*, Vol.26, No.30, (Jul 26, 2006), pp. (7870-7874), ISSN. 1529-2401 (Electronic)
- Lowy, M. T., Gault, L. & Yamamoto, B. K. (1993). Adrenalectomy Attenuates Stress-Induced Elevations in Extracellular Glutamate Concentrations in the Hippocampus. *J Neurochem*, Vol.61, No.5, (Nov, 1993), pp. (1957-1960), ISSN. 0022-3042 (Print)
- Lucassen, P. J., Vollmann-Honsdorf, G. K., Gleisberg, M., Czeh, B., De Kloet, E. R. & Fuchs, E. (2001). Chronic Psychosocial Stress Differentially Affects Apoptosis in Hippocampal Subregions and Cortex of the Adult Tree Shrew. *Eur J Neurosci*, Vol.14, No.1, (Jul, 2001), pp. (161-166), ISSN. 0953-816X (Print)
- Lucca, G., Comim, C. M., Valvassori, S. S., Reus, G. Z., Vuolo, F., Petronilho, F., Dal-Pizzol, F., Gavioli, E. C. & Quevedo, J. (2009). Effects of Chronic Mild Stress on the Oxidative Parameters in the Rat Brain. *Neurochem Int*, Vol.54, No.5-6, (May-Jun, 2009), pp. (358-362), ISSN. 1872-9754 (Electronic)
- Luine, V., Martinez, C., Villegas, M., Magarinos, A. M. & McEwen, B. S. (1996). Restraint Stress Reversibly Enhances Spatial Memory Performance. *Physiol Behav*, Vol.59, No.1, (Jan, 1996), pp. (27-32), ISSN. 0031-9384 (Print)
- Madrigal, J. L., Hurtado, O., Moro, M. A., Lizasoain, I., Lorenzo, P., Castrillo, A., Bosca, L. & Leza, J. C. (2002). The Increase in Tnf-Alpha Levels Is Implicated in Nf-Kappab Activation and Inducible Nitric Oxide Synthase Expression in Brain Cortex after Immobilization Stress. *Neuropsychopharmacology*, Vol.26, No.2, (Feb, 2002), pp. (155-163), ISSN. 0893-133X (Print)
- Madrigal, J. L., Moro, M. A., Lizasoain, I., Lorenzo, P., Castrillo, A., Bosca, L. & Leza, J. C. (2001). Inducible Nitric Oxide Synthase Expression in Brain Cortex after Acute Restraint Stress Is Regulated by Nuclear Factor Kappab-Mediated Mechanisms. *J Neurochem*, Vol.76, No.2, (Jan, 2001), pp. (532-538), ISSN. 0022-3042 (Print)
- Maes, M. (1995). Evidence for an Immune Response in Major Depression: A Review and Hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry*, Vol.19, No.1, (Jan, 1995), pp. (11-38), ISSN. 0278-5846 (Print)
- Magarinos, A. M. & McEwen, B. S. (1995). Stress-Induced Atrophy of Apical Dendrites of Hippocampal Ca3c Neurons: Involvement of Glucocorticoid Secretion and Excitatory Amino Acid Receptors. *Neuroscience*, Vol.69, No.1, (Nov, 1995), pp. (89-98), ISSN. 0306-4522 (Print)

- Magarinos, A. M., McEwen, B. S., Flugge, G. & Fuchs, E. (1996). Chronic Psychosocial Stress Causes Apical Dendritic Atrophy of Hippocampal Ca3 Pyramidal Neurons in Subordinate Tree Shrews. *J Neurosci*, Vol.16, No.10, (May 15, 1996), pp. (3534-3540), ISSN. 0270-6474 (Print)
- Makatsori, A., Duncko, R., Moncek, F., Loder, I., Katina, S. & Jezova, D. (2004). Modulation of Neuroendocrine Response and Non-Verbal Behavior During Psychosocial Stress in Healthy Volunteers by the Glutamate Release-Inhibiting Drug Lamotrigine. *Neuroendocrinology*, Vol.79, No.1, (Jan, 2004), pp. (34-42), ISSN. 0028-3835 (Print)
- Malberg, J. E. & Duman, R. S. (2003). Cell Proliferation in Adult Hippocampus Is Decreased by Inescapable Stress: Reversal by Fluoxetine Treatment. *Neuropsychopharmacology*, Vol.28, No.9, (Sep, 2003), pp. (1562-1571), ISSN. 0893-133X (Print)
- Manganas, L. N., Zhang, X., Li, Y., Hazel, R. D., Smith, S. D., Wagshul, M. E., Henn, F., Benveniste, H., Djuric, P. M., Enikolopov, G. & Maletic-Savatic, M. (2007). Magnetic Resonance Spectroscopy Identifies Neural Progenitor Cells in the Live Human Brain. *Science*, Vol.318, No.5852, (Nov 9, 2007), pp. (980-985), ISSN. 1095-9203 (Electronic)
- Manji, H. K., Moore, G. J. & Chen, G. (2000). Clinical and Preclinical Evidence for the Neurotrophic Effects of Mood Stabilizers: Implications for the Pathophysiology and Treatment of Manic-Depressive Illness. *Biol Psychiatry*, Vol.48, No.8, (Oct 15, 2000), pp. (740-754), ISSN. 0006-3223 (Print)
- Marcus, S. R., Nadiger, H. A., Chandrakala, M. V., Rao, T. I. & Sadasivudu, B. (1986). Acute and Short-Term Effects of Lithium on Glutamate Metabolism in Rat Brain. *Biochem Pharmacol*, Vol.35, No.3, (Feb 1, 1986), pp. (365-369), ISSN. 0006-2952 (Print)
- Martin, K. P. & Wellman, C. L. (2011). Nmda Receptor Blockade Alters Stress-Induced Dendritic Remodeling in Medial Prefrontal Cortex. *Cereb Cortex*, (Mar 7, 2011), pp. ISSN. 1460-2199 (Electronic)
- McEwen, B. S. (2004). Protection and Damage from Acute and Chronic Stress: Allostasis and Allostatic Overload and Relevance to the Pathophysiology of Psychiatric Disorders. *Ann N Y Acad Sci*, Vol.1032, (Dec, 2004), pp. (1-7), ISSN. 0077-8923 (Print)
- Melchior, M., Caspi, A., Milne, B. J., Danese, A., Poulton, R. & Moffitt, T. E. (2007). Work Stress Precipitates Depression and Anxiety in Young, Working Women and Men. *Psychol Med*, Vol.37, No.8, (Aug, 2007), pp. (1119-1129), ISSN. 0033-2917 (Print)
- Mill, J. & Petronis, A. (2007). Molecular Studies of Major Depressive Disorder: The Epigenetic Perspective. *Mol Psychiatry*, Vol.12, No.9, (Sep, 2007), pp. (799-814), ISSN. 1359-4184 (Print)
- Miller, J. C., Jimenez, P. & Mathe, A. A. (2007). Restraint Stress Influences Ap-1 and Creb DNA-Binding Activity Induced by Chronic Lithium Treatment in the Rat Frontal Cortex and Hippocampus. *Int J Neuropsychopharmacol*, Vol.10, No.5, (Oct, 2007), pp. (609-619), ISSN. 1461-1457 (Print)
- Miller, J. C. & Mathe, A. A. (1997). Basal and Stimulated C-Fos Mrna Expression in the Rat Brain: Effect of Chronic Dietary Lithium. *Neuropsychopharmacology*, Vol.16, No.6, (Jun, 1997), pp. (408-418), ISSN. 0893-133X (Print)
- Mirescu, C. & Gould, E. (2006). Stress and Adult Neurogenesis. *Hippocampus*, Vol.16, No.3, 2006, pp. (233-238), ISSN. 1050-9631 (Print)

- Moghaddam, B., Bolinao, M. L., Stein-Behrens, B. & Sapolsky, R. (1994). Glucocorticoids Mediate the Stress-Induced Extracellular Accumulation of Glutamate. *Brain Res*, Vol.655, No.1-2, (Aug 29, 1994), pp. (251-254), ISSN. 0006-8993 (Print)
- Nair, A., Vadodaria, K. C., Banerjee, S. B., Benekareddy, M., Dias, B. G., Duman, R. S. & Vaidya, V. A. (2007). Stressor-Specific Regulation of Distinct Brain-Derived Neurotrophic Factor Transcripts and Cyclic Amp Response Element-Binding Protein Expression in the Postnatal and Adult Rat Hippocampus. *Neuropsychopharmacology*, Vol.32, No.7, (Jul, 2007), pp. (1504-1519), ISSN. 0893-133X (Print)
- Nocjar, C., Hammonds, M. D. & Shim, S. S. (2007). Chronic Lithium Treatment Magnifies Learning in Rats. *Neuroscience*, Vol.150, No.4, (Dec 19, 2007), pp. (774-788), ISSN. 0306-4522 (Print)
- Oitzl, M. S., Flutterm, M., Sutanto, W. & de Kloet, E. R. (1998). Continuous Blockade of Brain Glucocorticoid Receptors Facilitates Spatial Learning and Memory in Rats. *Eur J Neurosci*, Vol.10, No.12, (Dec, 1998), pp. (3759-3766), ISSN. 0953-816X (Print)
- Olivenza, R., Moro, M. A., Lizasoain, I., Lorenzo, P., Fernandez, A. P., Rodrigo, J., Bosca, L. & Leza, J. C. (2000). Chronic Stress Induces the Expression of Inducible Nitric Oxide Synthase in Rat Brain Cortex. *J Neurochem*, Vol.74, No.2, (Feb, 2000), pp. (785-791), ISSN. 0022-3042 (Print)
- Pavlidis, C., Kimura, A., Magarinos, A. M. & McEwen, B. S. (1994). Type I Adrenal Steroid Receptors Prolong Hippocampal Long-Term Potentiation. *Neuroreport*, Vol.5, No.18, (Dec 20, 1994), pp. (2673-2677), ISSN. 0959-4965 (Print)
- Pavlidis, C., Kimura, A., Magarinos, A. M. & McEwen, B. S. (1995). Hippocampal Homosynaptic Long-Term Depression/Depotentiation Induced by Adrenal Steroids. *Neuroscience*, Vol.68, No.2, (Sep, 1995), pp. (379-385), ISSN. 0306-4522 (Print)
- Perisic, T., Zimmermann, N., Kirmeier, T., Asmus, M., Tuorto, F., Uhr, M., Holsboer, F., Rein, T. & Zschocke, J. (2010). Valproate and Amitriptyline Exert Common and Divergent Influences on Global and Gene Promoter-Specific Chromatin Modifications in Rat Primary Astrocytes. *Neuropsychopharmacology*, Vol.35, No.3, (Feb, 2010), pp. (792-805), ISSN. 1740-634X (Electronic)
- Petronis, A. (2003). Epigenetics and Bipolar Disorder: New Opportunities and Challenges. *Am J Med Genet C Semin Med Genet*, Vol.123C, No.1, (Nov 15, 2003), pp. (65-75), ISSN. 1552-4868 (Print)
- Pham, K., Nacher, J., Hof, P. R. & McEwen, B. S. (2003). Repeated Restraint Stress Suppresses Neurogenesis and Induces Biphasic Psa-Ncam Expression in the Adult Rat Dentate Gyrus. *Eur J Neurosci*, Vol.17, No.4, (Feb, 2003), pp. (879-886), ISSN. 0953-816X (Print)
- Phiel, C. J. & Klein, P. S. (2001). Molecular Targets of Lithium Action. *Annu Rev Pharmacol Toxicol*, Vol.41, 2001, pp. (789-813), ISSN. 0362-1642 (Print)
- Pittenger, C. & Duman, R. S. (2008). Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms. *Neuropsychopharmacology*, Vol.33, No.1, (Jan, 2008), pp. (88-109), ISSN. 0893-133X (Print)
- Post, R. M., Ketter, T. A., Pazzaglia, P. J., Denicoff, K., George, M. S., Callahan, A., Leverich, G. & Frye, M. (1996). Rational Polypharmacy in the Bipolar Affective Disorders. *Epilepsy Res Suppl*, Vol.11, 1996, pp. (153-180), ISSN. 0922-9833 (Print)

- Radley, J. J., Sisti, H. M., Hao, J., Rocher, A. B., McCall, T., Hof, P. R., McEwen, B. S. & Morrison, J. H. (2004). Chronic Behavioral Stress Induces Apical Dendritic Reorganization in Pyramidal Neurons of the Medial Prefrontal Cortex. *Neuroscience*, Vol.125, No.1, 2004), pp. (1-6), ISSN. 0306-4522 (Print)
- Rao, J. S., Bazinet, R. P., Rapoport, S. I. & Lee, H. J. (2007a). Chronic Treatment of Rats with Sodium Valproate Downregulates Frontal Cortex Nf-KappaB DNA Binding Activity and Cox-2 Mrna. *Bipolar Disord*, Vol.9, No.5, (Aug, 2007a), pp. (513-520), ISSN. 1398-5647 (Print)
- Rao, J. S., Ertley, R. N., DeMar, J. C., Jr., Rapoport, S. I., Bazinet, R. P. & Lee, H. J. (2007b). Dietary N-3 Pufa Deprivation Alters Expression of Enzymes of the Arachidonic and Docosahexaenoic Acid Cascades in Rat Frontal Cortex. *Mol Psychiatry*, Vol.12, No.2, (Feb, 2007b), pp. (151-157), ISSN. 1359-4184 (Print)
- Rao, J. S., Ertley, R. N., Lee, H. J., DeMar, J. C., Jr., Arnold, J. T., Rapoport, S. I. & Bazinet, R. P. (2007c). N-3 Polyunsaturated Fatty Acid Deprivation in Rats Decreases Frontal Cortex Bdnf Via a P38 Mapk-Dependent Mechanism. *Mol Psychiatry*, Vol.12, No.1, (Jan, 2007c), pp. (36-46), ISSN. 1359-4184 (Print)
- Rao, J. S., Lee, H. J., Rapoport, S. I. & Bazinet, R. P. (2008). Mode of Action of Mood Stabilizers: Is the Arachidonic Acid Cascade a Common Target? *Mol Psychiatry*, Vol.13, No.6, (Jun, 2008), pp. (585-596), ISSN. 1476-5578 (Electronic)
- Reznikov, L. R., Grillo, C. A., Piroli, G. G., Pasumarthi, R. K., Reagan, L. P. & Fadel, J. (2007). Acute Stress-Mediated Increases in Extracellular Glutamate Levels in the Rat Amygdala: Differential Effects of Antidepressant Treatment. *Eur J Neurosci*, Vol.25, No.10, (May, 2007), pp. (3109-3114), ISSN. 0953-816X (Print)
- Rosenbrock, H., Koros, E., Bloching, A., Podhorna, J. & Borsini, F. (2005). Effect of Chronic Intermittent Restraint Stress on Hippocampal Expression of Marker Proteins for Synaptic Plasticity and Progenitor Cell Proliferation in Rats. *Brain Res*, Vol.1040, No.1-2, (Apr 8, 2005), pp. (55-63), ISSN. 0006-8993 (Print)
- Roth, T. L., Lubin, F. D., Funk, A. J. & Sweatt, J. D. (2009). Lasting Epigenetic Influence of Early-Life Adversity on the Bdnf Gene. *Biol Psychiatry*, Vol.65, No.9, (May 1, 2009), pp. (760-769), ISSN. 1873-2402 (Electronic)
- Roth, T. L., Zoladz, P. R., Sweatt, J. D. & Diamond, D. M. (2011). Epigenetic Modification of Hippocampal Bdnf DNA in Adult Rats in an Animal Model of Post-Traumatic Stress Disorder. *J Psychiatr Res*, Vol.45, No.7, (Jul, 2011), pp. (919-926), ISSN. 1879-1379 (Electronic)
- Sapolsky, R. M. (2003). Stress and Plasticity in the Limbic System. *Neurochem Res*, Vol.28, No.11, (Nov, 2003), pp. (1735-1742), ISSN. 0364-3190 (Print)
- Schloesser, R. J., Huang, J., Klein, P. S. & Manji, H. K. (2008). Cellular Plasticity Cascades in the Pathophysiology and Treatment of Bipolar Disorder. *Neuropsychopharmacology*, Vol.33, No.1, (Jan, 2008), pp. (110-133), ISSN. 0893-133X (Print)
- Schmidt-Hieber, C., Jonas, P. & Bischofberger, J. (2004). Enhanced Synaptic Plasticity in Newly Generated Granule Cells of the Adult Hippocampus. *Nature*, Vol.429, No.6988, (May 13, 2004), pp. (184-187), ISSN. 1476-4687 (Electronic)
- Shaltiel, G., Chen, G. & Manji, H. K. (2007). Neurotrophic Signaling Cascades in the Pathophysiology and Treatment of Bipolar Disorder. *Curr Opin Pharmacol*, Vol.7, No.1, (Feb, 2007), pp. (22-26), ISSN. 1471-4892 (Print)

- Shao, L., Young, L. T. & Wang, J. F. (2005). Chronic Treatment with Mood Stabilizers Lithium and Valproate Prevents Excitotoxicity by Inhibiting Oxidative Stress in Rat Cerebral Cortical Cells. *Biol Psychiatry*, Vol.58, No.11, (Dec 1, 2005), pp. (879-884), ISSN. 0006-3223 (Print)
- Shim, S. S., Hammonds, M. D., Ganocy, S. J. & Calabrese, J. R. (2007). Effects of Sub-Chronic Lithium Treatment on Synaptic Plasticity in the Dentate Gyrus of Rat Hippocampal Slices. *Prog Neuropsychopharmacol Biol Psychiatry*, Vol.31, No.2, (Mar 30, 2007), pp. (343-347), ISSN. 0278-5846 (Print)
- Shors, T. J. & Dryver, E. (1994). Effect of Stress and Long-Term Potentiation (Ltp) on Subsequent Ltp and the Theta Burst Response in the Dentate Gyrus. *Brain Res*, Vol.666, No.2, (Dec 15, 1994), pp. (232-238), ISSN. 0006-8993 (Print)
- Shors, T. J., Seib, T. B., Levine, S. & Thompson, R. F. (1989). Inescapable Versus Escapable Shock Modulates Long-Term Potentiation in the Rat Hippocampus. *Science*, Vol.244, No.4901, (Apr 14, 1989), pp. (224-226), ISSN. 0036-8075 (Print)
- Silva, R., Martins, L., Longatto-Filho, A., Almeida, O. F. & Sousa, N. (2007). Lithium Prevents Stress-Induced Reduction of Vascular Endothelium Growth Factor Levels. *Neurosci Lett*, Vol.429, No.1, (Dec 11, 2007), pp. (33-38), ISSN. 0304-3940 (Print)
- Silva, R., Mesquita, A. R., Bessa, J., Sousa, J. C., Sotiropoulos, I., Leao, P., Almeida, O. F. & Sousa, N. (2008). Lithium Blocks Stress-Induced Changes in Depressive-Like Behavior and Hippocampal Cell Fate: The Role of Glycogen-Synthase-Kinase-3 β . *Neuroscience*, Vol.152, No.3, (Mar 27, 2008), pp. (656-669), ISSN. 0306-4522 (Print)
- Son, H., Yu, I. T., Hwang, S. J., Kim, J. S., Lee, S. H., Lee, Y. S. & Kaang, B. K. (2003). Lithium Enhances Long-Term Potentiation Independently of Hippocampal Neurogenesis in the Rat Dentate Gyrus. *J Neurochem*, Vol.85, No.4, (May, 2003), pp. (872-881), ISSN. 0022-3042 (Print)
- Song, C., Li, X., Kang, Z. & Kadotomi, Y. (2007). Omega-3 Fatty Acid Ethyl-Eicosapentaenoate Attenuates IL-1 β -Induced Changes in Dopamine and Metabolites in the Shell of the Nucleus Accumbens: Involved with PLA2 Activity and Corticosterone Secretion. *Neuropsychopharmacology*, Vol.32, No.3, (Mar, 2007), pp. (736-744), ISSN. 0893-133X (Print)
- Sousa, N., Lukoyanov, N. V., Madeira, M. D., Almeida, O. F. & Paula-Barbosa, M. M. (2000). Reorganization of the Morphology of Hippocampal Neurites and Synapses after Stress-Induced Damage Correlates with Behavioral Improvement. *Neuroscience*, Vol.97, No.2, 2000, pp. (253-266), ISSN. 0306-4522 (Print)
- Stahl, S. M. *Stahl's Essential Psychopharmacology : Neuroscientific Basis and Practical Applications* (3rd ed, Fully rev. and expanded.), Cambridge University Press, ISBN. 9780521857024 (hardcover), Cambridge ; New York
- Tashiro, A., Sandler, V. M., Toni, N., Zhao, C. & Gage, F. H. (2006). NMDA-Receptor-Mediated, Cell-Specific Integration of New Neurons in Adult Dentate Gyrus. *Nature*, Vol.442, No.7105, (Aug 24, 2006), pp. (929-933), ISSN. 1476-4687 (Electronic)
- Thomas, R. M., Hotsonpiller, G. & Peterson, D. A. (2007). Acute Psychosocial Stress Reduces Cell Survival in Adult Hippocampal Neurogenesis without Altering Proliferation. *J Neurosci*, Vol.27, No.11, (Mar 14, 2007), pp. (2734-2743), ISSN. 1529-2401 (Electronic)
- Tsankova, N., Renthal, W., Kumar, A. & Nestler, E. J. (2007). Epigenetic Regulation in Psychiatric Disorders. *Nat Rev Neurosci*, Vol.8, No.5, (May, 2007), pp. (355-367), ISSN. 1471-003X (Print)

- Umka, J., Mustafa, S., ElBeltagy, M., Thorpe, A., Latif, L., Bennett, G. & Wigmore, P. M. (2010). Valproic Acid Reduces Spatial Working Memory and Cell Proliferation in the Hippocampus. *Neuroscience*, Vol.166, No.1, (Mar 10, 2010), pp. (15-22), ISSN. 1873-7544 (Electronic)
- Vaher, P. R., Luine, V. N., Gould, E. & McEwen, B. S. (1994). Effects of Adrenalectomy on Spatial Memory Performance and Dentate Gyrus Morphology. *Brain Res*, Vol.656, No.1, (Sep 5, 1994), pp. (71-78), ISSN. 0006-8993 (Print)
- van, I. M. H., Caspers, K., Bakermans-Kranenburg, M. J., Beach, S. R. & Philibert, R. (2010). Methylation Matters: Interaction between Methylation Density and Serotonin Transporter Genotype Predicts Unresolved Loss or Trauma. *Biol Psychiatry*, Vol.68, No.5, (Sep 1, 2010), pp. (405-407), ISSN. 1873-2402 (Electronic)
- Vasconcellos, A. P., Tabajara, A. S., Ferrari, C., Rocha, E. & Dalmaz, C. (2003). Effect of Chronic Stress on Spatial Memory in Rats Is Attenuated by Lithium Treatment. *Physiol Behav*, Vol.79, No.2, (Jul, 2003), pp. (143-149), ISSN. 0031-9384 (Print)
- Vyas, A., Jadhav, S. & Chattarji, S. (2006). Prolonged Behavioral Stress Enhances Synaptic Connectivity in the Basolateral Amygdala. *Neuroscience*, Vol.143, No.2, (Dec 1, 2006), pp. (387-393), ISSN. 0306-4522 (Print)
- Vyas, A., Mitra, R., Shankaranarayana Rao, B. S. & Chattarji, S. (2002). Chronic Stress Induces Contrasting Patterns of Dendritic Remodeling in Hippocampal and Amygdaloid Neurons. *J Neurosci*, Vol.22, No.15, (Aug 1, 2002), pp. (6810-6818), ISSN. 1529-2401 (Electronic)
- Watanabe, Y., Gould, E. & McEwen, B. S. (1992). Stress Induces Atrophy of Apical Dendrites of Hippocampal CA3 Pyramidal Neurons. *Brain Res*, Vol.588, No.2, (Aug 21, 1992), pp. (341-345), ISSN. 0006-8993 (Print)
- Wood, G. E., Young, L. T., Reagan, L. P., Chen, B. & McEwen, B. S. (2004). Stress-Induced Structural Remodeling in Hippocampus: Prevention by Lithium Treatment. *Proc Natl Acad Sci U S A*, Vol.101, No.11, (Mar 16, 2004), pp. (3973-3978), ISSN. 0027-8424 (Print)
- Xu, H., Chen, Z., He, J., Haimanot, S., Li, X., Dyck, L. & Li, X. M. (2006). Synergetic Effects of Quetiapine and Venlafaxine in Preventing the Chronic Restraint Stress-Induced Decrease in Cell Proliferation and Bdnf Expression in Rat Hippocampus. *Hippocampus*, Vol.16, No.6, 2006), pp. (551-559), ISSN. 1050-9631 (Print)
- Xu, L., Anwyl, R. & Rowan, M. J. (1997). Behavioural Stress Facilitates the Induction of Long-Term Depression in the Hippocampus. *Nature*, Vol.387, No.6632, (May 29, 1997), pp. (497-500), ISSN. 0028-0836 (Print)
- Yang, C. H., Huang, C. C. & Hsu, K. S. (2004). Behavioral Stress Modifies Hippocampal Synaptic Plasticity through Corticosterone-Induced Sustained Extracellular Signal-Regulated Kinase/Mitogen-Activated Protein Kinase Activation. *J Neurosci*, Vol.24, No.49, (Dec 8, 2004), pp. (11029-11034), ISSN. 1529-2401 (Electronic)
- Yurgelun-Todd, D. A., Gruber, S. A., Kanayama, G., Killgore, W. D., Baird, A. A. & Young, A. D. (2000). fMRI During Affect Discrimination in Bipolar Affective Disorder. *Bipolar Disord*, Vol.2, No.3 Pt 2, (Sep, 2000), pp. (237-248), ISSN. 1398-5647 (Print)

Bipolar Disorder - A Portrait of a Complex Mood Disorder

Edited by Dr. Jarrett Barnhill

ISBN 978-953-51-0002-7

Hard cover, 236 pages

Publisher InTech

Published online 24, February, 2012

Published in print edition February, 2012

Bipolar Disorder: Portrait of a Complex Mood Disorder is a step towards integrating many diverse perspectives on BD. As we shall see, such diversity makes it difficult to clearly define the boundaries of BD. It is helpful to view BD from this perspective, as a final common pathway arises from multiple frames of reference. The integration of epigenetics, molecular pharmacology, and neurophysiology is essential. One solution involves using this diverse data to search for endophenotypes to aid researchers, even though most clinicians prefer broader groupings of symptoms and clinical variables. Our challenge is to consolidate this new information with existing clinical practice in a usable fashion. This need for convergent thinkers who can integrate the findings in this book remains a critical need. This book is a small step in that direction and hopefully guides researchers and clinicians towards a new synthesis of basic neurosciences and clinical psychiatry

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Young-Ki Chung and Seungmin Yoo (2012). Anti-Stress Effects of Mood Stabilizers and Relevance to Their Therapeutic Actions, Bipolar Disorder - A Portrait of a Complex Mood Disorder, Dr. Jarrett Barnhill (Ed.), ISBN: 978-953-51-0002-7, InTech, Available from: <http://www.intechopen.com/books/bipolar-disorder-a-portrait-of-a-complex-mood-disorder/anti-stress-effects-of-mood-stabilizers->

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen