Systematic hypothesis for post-stroke depression caused inflammation and neurotransmission and resultant on possible treatments

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Abstract
Post-stroke depression (PSD) is a prevalent complex psychiatric disorder that causes delay to functional recovery from rehabilitation and also increases cognitive impairment. The etiology of PSD remains controversial and appears to be physical and psycho-social in origin, alone or in combination. The causes of PSD as well as the mechanisms conferring beneficial antidepressant effects in the context of ischemic brain injury are still unknown. In addition, appropriate treatment strategies for therapy to prevent stroke-induced depression-like behavior remain to be developed. This paper, therefore, proposes two hypotheses for post-stroke depression: The inflammatory hypothesis, which is the increased production of proinflammatory cytokines resulting from brain ischemia in cerebral areas causing the pathogenesis of post-stroke depression and the glutamate hypothesis, where the excess glucocorticoids released from stress-induced over-activation of hypothalamus-pituitary-adrenal (HPA) lead to dysfunction of glutamatergic transmission. Neurotrophins, especially brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) both play various roles in the central nervous system (CNS), attenuate apoptosis in cultured neurons, stimulate neurogenesis and increase survival and protect neuronal tissues from cell death induced by ischemia or depression. We also touch upon recent treatment strategies including inhibition of pro-inflammatory cytokines, SSRI, neurotrophins and cell-based therapies. In the present review, we provide an overview of recent evidence concerning the mechanisms of post-stroke depression and propose four prospective treatment strategies so as to provide references for clinical evidence-based medications.

INTRODUCTION
Post-stroke depression (PSD) occurs in approximately one-third of stroke survivors and is one of the more serious complications of a stroke. Post-stroke depression generally runs a chronic course and victims of post-stroke depression show a variety of adverse health outcomes including pessimism and disappointment, losing the hope of recovery, rejecting the project of rehabilitation measures, refusing to eat and despair to the degree of suicide, which all seriously affect the prognosis.
of the patient. PSD has the potential to affect the ever-increasing number of stroke survivors and their recovery (Wang et al. 2009). PSD has gradually aroused people’s attention because of its high morbidity and mortality.

Depression after stroke is caused by a variety of reasons, which include the interaction of biological, psychological and social factors. Common mood symptoms after stroke include anxiety and feelings of despair as well as anhedonia (Loubinoux et al. 2012). Physical damage of the brain leads to impaired function of the brain. It has been shown that ischemic insults directly affect neural circuits involved in mood regulation, with social and psychological influences.

Their cognitive or locomotive impairment associated with stroke may be the underlying biological or psychological cause of depression (El Hachioui et al. 2013). The victims of PSD presented clinically with aphasia, anhedonia and anosognosia. Post-stroke depression is considered to be caused by neurotransmitter changes in the brain after cerebrovascular accident (Pustokhanova & Morozova 2013). Among several hypothesis about the pathogenesis of depression, low 5-HT function has been considered to be the main cause of depression, the development of antidepressant treatment strategy against the low level of brain 5-HT, such as selective serotonin reuptake inhibitors (SSRIs) have been widely used clinically. Psychological and social factors also play important role in the resulting in depression after stroke.

Antidepressant treatment initiated soon after stroke may prevent the emergence of PSD (Robinson et al. 2008). A series of studies has also reported beneficial effects of antidepressant pharmacotherapy on long term functional recovery like the activities of daily living as well as cognitive and executive recovery following stroke (Narushima et al. 2007; Jorge et al. 2010; Acler et al. 2009). Of note, proper antidepressant effects may even extend beyond mood symptoms, to motor recovery, which significantly reduce the proportion of patients reaching only partial or full dependence (Chollet et al. 2011). Moreover, a placebo-controlled clinical trial of antidepressant pharmacotherapy early in the recovery period after stroke demonstrated a significant advantage of active antidepressant treatment in terms of patients’ survival, compared with patients who did not receive such treatment, regardless of whether they were initially depressed. Importantly, the beneficial effect of antidepressants remained significant after the effects of age, stroke type, coexistent diabetes mellitus, and occurrence of a depressive disorder with a relapsing course were controlled (Jorge et al. 2003).

However, some patients may be more disturbed than others by specific side-effects such as sedation, decrease of blood pressure, indigestion, increase of weight or sexual dysfunction. This often results in patients’ poor compliance, and then subsequent discontinuing of treatment leads to recurrence of depressive symptoms and increased suicidal risk (Keller et al. 2002).

Therefore, the prevention of post-stroke depressive episodes by new treatments based on understood physiological mechanisms may well replace the existing methods to treat PSD – serotonin and noradrenaline reuptake inhibition. In this review, an attempt is made to overview molecular concepts of the disease from three aspects: the inflammatory hypothesis, neurotrophins and the glutamate hypothesis. In addition to this four perspectives on possible treatment strategies are considered, so as to provide reference for future clinical evidence-based medications.

**INFLAMMATORY FACTORS**

Clinical post-stroke depression and sickness behavior occur in response to nearly all physiological and psychological stressors after stroke. Sickness behavior is characterized by reduction in locomotor activity, behavioral inhibition, disinterest in social interactions, exploration and grooming, reduction of reproductive performance and anhedonia, somnolence and sleepiness, anorexia and weight loss, slower thoughts, failure to concentrate and anxiety, hopelessness and inferiority complex (Lang & Borgwardt 2013). This behavior has been proved to be mediated by pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, IL-8, IL-18, tumor necrosis factor-α (TNF-α), interferon-α (IFN-α) and IFN-γ, which are resulted from stroke and may lead to an amplification of the inflammatory process, particularly in limbic areas (Spalletta et al. 2006).

Several perspectives have been offered to account for how inflammatory factors might promote brain neurochemical changes that lead to depression and reported prominent changes in proinflammatory cytokines following stroke. For example, the increased production of pro-inflammatory cytokines such as Interleukin-1β (IL-1β) and TNF-α have been hypothesized to play an important role in neurodegeneration and CNS inflammation (Allan & Rothwell 2001; Kostulas et al. 1999). IL-6 cytokine has been associated with acute inflammatory response after stroke and correlated with severity and clinical outcome of stroke (Smith et al. 2004). As a marker of cardiovascular diseases, IL-18 leads to growth and vulnerability of atherosclerotic plaques, and therefore it could likely participate in the development of ischemic brain injury, as found in hypoxic-ischemic animal models, and in focal ischemia in humans (Felderhoff-Mueser et al. 2005). In addition, the IL-8 is involved in the recruitment of inflammatory cells and amplification of the secondary inflammatory process following stroke (Grau et al. 2001). Molecules released from injured or dying brain cells can be detected by increased toll-like receptors (TLRs) as danger signals’ triggering NF-κB-dependent inflammatory signaling and contribute to the inflammatory response (Oppenheim & Yang 2005; Wang et al. 2007). These cytokines can interact with virtually every pathophysiologic domain relevant to...
Depression (Dantzer et al. 2011; Maes et al. 2011). In humans, decreased hippocampal volume, maladaptive structural and functional changes in hippocampal circuitry, and dysfunctions of glutamatergic neurotransmission have been associated with stress-related disorders. Modulated by stress hormones, the hippocampus is one of the major brain areas that exert strong regulatory control over the HPA axis. Abnormalities in the HPA system are suggested to contribute to the pathology of depression (Ising et al. 2005). HPA system activation is known as one of the endocrinological coping mechanisms against stressful stimuli.

As one of the major brain areas, the hippocampus exerts strong regulatory control over the HPA axis. The hippocampus has direct and indirect polysynaptic connections to the paraventricular nucleus (PVN), and it negatively influences the HPA axis via GR-dependent negative feedback. In rats and humans, hippocampus stimulation decreases glucocorticoid level, especially during the stress recovery phase, which is the most reliant on negative feedback. As a result, the possible

NEUROTROPHIN SIGNALING

Neurotrophins are a group of molecules that promote the development and survival of neurons. In the context of mood disorders, brain-derived neurotrophic factor (BDNF) and VEGF have attracted extensive attention. An increased BDNF level can be observed in a brain on antidepressants, and BDNF produces antidepressant effects in the model of depression. BDNF is an attractive candidate molecule to explain the complex interaction between depression, antidepressants and post-stroke recovery. Firstly, BDNF plays multiple roles in the central nervous system (CNS), including maintaining cell survival and regulation of synaptic function in depressive behaviors. Secondly BDNF has been suggested to protect against ischemic brain injury and attenuate apoptosis in cultured neurons after glucose deprivation. Thirdly, BDNF can reduce infarct volume after stroke and promote hippocampal neurogenesis (Zhang & Pardridge 2006). Furthermore, in CNS neurons, BDNF influences neuronal cells beneficently through these intracellular signaling cascades through triggering mitogen-activated protein/extracellular signal-regulated kinase (MAPK/ERK), activation of phospholipaseCc (PLCc), and phosphoinositide 3-kinase (PI3K)/Akt pathway (Numakawa et al. 2013).

Whether antidepressant treatment is able to increase BDNF levels in all the ischemic lesions and whether BDNF expression in a particular brain area is especially involved in the pathogenesis of PSD both require further research.

VEGF is an endothelial cell mitogen and survival factor that regulates vascular function, but is also expressed in the brain and exerts a large number of diverse neuronal effects in the central and peripheral nervous system. VEGF stimulates neurogenesis, promotes growth of neurons and glial cells, increases survival and protects neuronal tissues from cell death induced by ischemia or depression. Increased VEGF levels can be observed in patients with depression and antidepressant treatment reverses these effects. Moreover, the local administration of this trophic factor produces an increase in hippocampal proliferation and these neurovascular trophic signals may also influence mechanisms of recovery after stroke. Even though this data indicates the importance of VEGF brain levels in the ischemic stroke and depressive disorder, preliminary reports do not show a clear correlation among peripheral VEGF, ischemic stroke and depressive disorders.

GLUTAMATE HYPOTHESIS

The glutamate hypothesis for depression, for which hippocampus dysfunction is a major component, is well accepted (Sanacora et al. 2012). In humans, decreased hippocampal volume, maladaptive structural and functional changes in hippocampal circuitry, and dysfunctions of glutamatergic neurotransmission have been associated with stress-related disorders. Modulated by stress hormones, the hippocampus is one of the major brain areas that exert strong regulatory control over the HPA axis. Abnormalities in the HPA system are suggested to contribute to the pathology of depression (Ising et al. 2005). HPA system activation is known as one of the endocrinological coping mechanisms against stressful stimuli.
involvement of increased glucocorticoid levels due to dysfunction of the hippocampus and HPA-axis, including GR downregulation in depressive disorders, has been speculate (Numakawa et al. 2013; Ising et al. 2005).

Glucocorticoids, which are critical stress hormones, influence neuronal function in the CNS, and are putatively involved in the onset of depression and stroke when levels are abnormally high. Increasing evidence indicates that glucocorticoids (GCs), produced in response to physical/emotional stressors, can exacerbate brain damage resulting from cerebral ischemia and severe seizure activity (Smith-Swintosky et al. 1996). Glucocorticoids are involved in neurodegenerative processes. While some date indicates that chronic elevation of circulating levels of GCs alone can result in neuronal degeneration in the hippocampus, particularly in aged animals, the most striking effects of GCs are observed when the brain is subjected to excitotoxic/metabolic insults (Franklin et al. 2012). The mechanisms underlying stress are not fully understood, but may involve the action of glucocorticoids on cells neighboring newly generated neurons. Glucocorticoids may also act by increasing glutamatergic transmission through increased glutamate release and NMDA receptor-dependent excitatory input from the entorhinal cortex onto newly generated neurons. Over-activation of NMDA receptors induces acute excitotoxicity, but without NMDA signaling, chronic neuronal remodeling cannot take place (Franklin et al. 2012).

These findings indicate that endogenous corticosterone contributes to the basal level of brain injury resulting from cerebral ischemia and depression and this in turn suggests that drugs suppressing glucocorticoid production and enforcing adult hippocampal neurogenesis may be effective in reducing brain damage in PSD patients.

TREATMENTS

Antidepressant treatment initiated soon after stroke may prevent the emergence of PSD. A number of studies have also reported the beneficial effects of antidepressant pharmacotherapy on long-term functional recovery after stroke including activities of daily living as well as cognitive and executive functioning (Akhdadzadeh et al. 2009).

The inhibitor of pro-inflammatory cytokine

As one of the main biological theories of PSD, the inflammation hypothesis has gained extensive attention. The inflammatory factors contribution to depression was based on findings that circulating cytokines, i.e., signaling molecules of the immune system, and other inflammatory factors, increased in depressed patients. Many people who were administered inflammatory cytokines such as interferon-α develop symptoms of depressed mood, anxiety and cognitive dysfunction, which cannot be distinguished from depression in the non-medically ill populations.

The importance of the inflammation hypothesis of post-stroke depression lies in raising the possibility that psychotropic drugs that have a central anti-inflammatory action might provide a new generation of antidepressants. And the possibility that depression is not just a psychiatric disorders but rather a consequence of physical illness has haunted medicine for a long time. Both experimental and clinical evidence shows that a rise in glucocorticoids might lead to an increase in pro-inflammatory cytokines and these might in turn contribute to the behavioral changes associated with depression.

Chronic treatment with sesamol, which is a potent inhibitor of cytokine production as well as an antioxidant, significantly reversed the unpredictable chronic stress-induced behavioral (increased immobility period, reduced sucrose preference) and inflammation surge (serum TNF-α) in stressed mice. In other words, sesamol may have the potential to exert antidepressant effects (Kumar et al. 2011). Also celecoxib, which is a Cyclooxygenase-2 inhibitor, was supposed to reduce the production of pro-inflammatory cytokines. It can be a potent effective adjuvant agent in the management of patients with major depression, because celecoxib treatment has been reported to reverse chronic unpredictable stress-induced depressive-like behavior (Chung et al. 2010). Statins have anti-inflammatory properties and accordingly, the use of statins was associated with a significant reduction in the risk of depression in individuals who have had a cardiac event in a prospective clinical trial. Though administering inflammatory cytokines can develop symptoms of depression, exclusive use of anti-inflammatory agents cannot cure the neurological diseases completely. Thus, ancillary drugs are needed to be discovered to cooperate with anti-inflammatory to help depressed patients.

SSRIs

Treatment of PSD with selective serotonin reuptake inhibitors (SSRIs) has produced encouraging results, considerable variability in the response to SSRIs has been noted among patients affected by PSD. Increased concentration of 5-HT in the synaptic gap after treatment of SSRIs can strengthen neurotransmission function, promote the recovery of injured neurons and prevent further nerve damage. Abnormalities of HPA system function normally after treatment with an antidepressant, and the GR level almost recovers as well. Antidepressants such as the commonly prescribed selective serotonin reuptake inhibitors (SSRIs), i.e., fluoxetine and citalopram can improve stroke outcome, favor neurogenesis and prevent the degeneration of dopaminergic neurons in depressed patients. This was accompanied by marked repression of microglia activation, neutrophil infiltration and expression of pro-inflammatory markers and improvement of
motor impairment and neurological deficits (Chung et al. 2011). The administration of pindolol with serotonin reuptake inhibitors can accelerate and enhance of the efficiency of antidepressant treatment, and a quicker and more pronounced decrease of symptoms in patients with nonresistant major depressive disorder was observed (Portella et al. 2011). What is particularly encouraging in the study of SSRIs is the lack of serious side effects and the high compliance of patients with appropriate medication. SSRIs might be a successful new treatment of post-stroke depression.

Neurotrophins and other neurotrophic factors

Neurotrophins and other neurotrophic factors have been shown to support the survival and differentiation of many neuronal populations of the central and peripheral nervous system. Growth factors such as BDNF, NGF, FGF, and GDNF have all met with variable degrees of success in animal models of stroke. Therefore, administering neurotrophic factors could be a promising strategy for the treatment of acute and chronic mild brain disorders. However, the delivery of neurotrophic factors to the brain is one of the largest obstacles in the development of effective therapy for neurodegenerative disorders, because these proteins are not able to cross the blood-brain barrier (Semkova & Krieglstein 1999). However, some alternatives may yet exist, such as smaller peptides, transnasal delivery of growth factors to bypass the blood-brain barrier, peptide mimetics and compounds that can induce growth factor synthesis but do not require direct infusion into brain (Zhang & Chopp 2009). In fact, αβ-adrenoceptor agonist, one kind of lipophilic drugs, has been proved to increase endogenous nerve growth factor NGF synthesis in the brain (Semkova & Krieglstein 1999). It needs further research in applying neurotrophins and other neurotrophic factors to post-stroke therapy, while the other alternatives to increase the production may be a definitely decent way.

Cell-based therapies

Although stroke-damaged brain usually exhibits varying degrees of spontaneous recovery, there will always be significant areas where endogenous repair is insufficient. In this regard, cell-based therapies may represent a new frontier. To date, a variety of cell sources have been tested in neurological diseases, including neural stem cells, bone-marrow-derived mesenchymal cells, as well endothelial progenitor cells (Koch et al. 2009).

Endothelial cells are known to modulate neurogenesis, in part, through the secretion of soluble factors including NGF, BDNF and VEGF, several of which are also known to be synthesized by neuronal cells and modulated by endothelial cells, suggesting a complex, dynamic cross-talk between endothelial cells and neuronal cells including neural stem cells (Doetsch 2003). As neural stem cells can be isolated from various regions of the adult brain including post-mortem tissue, clonally expanded in vitro, perhaps genetically modified and/or induced to differentiate into cell lineages of the CNS, they have become powerful prospective candidates for enhancing or repairing the functional quality of neural tissue in many CNS related diseases (Feldmann Jr & Mattern 2006). Infarcted brain tissue releases and up-regulates various chemokines to attract stem and precursor cell populations (Madri 2009). Induced pluripotent stem cells may also provide an alternative cell source to embryonic stem cells (Takahashi & Yamanaka 2006). Treatments have typically involved direct transplantations into brain parenchyma, catheter infusions into cerebral ventricles, as well as systemic injections into circulating blood.

One advantage of cell-based therapies is the theoretical possibility that cell repair can be custom designed to suit specific diseases or individual needs. Whether similar methods can be applied to post-stroke depression victims remains to be researched deeply. Overall, cell-based therapies in models of experimental stroke suggest that delayed repair is a viable treatment approach. But more work is needed to translate these promising results into effective therapies. Many questions remain, and the precise mechanisms of cell-induced repair are still unclear.

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REFERENCES