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Review

Could neuroplasticity be an answer to different antidepressants efficacy among individuals?

Z. H. Zheng[1]*, Y. T. Zeng[2], J. H. Tao[1], J. J. Duan[3], T. Zhou[3] and F. Xu[3]*

[1]Guangdong Province Pharmaceutical Association, Guangzhou, China.
[2]Guangdong General Hospital, Guangdong Academy of Medical Science, Guangzhou, China.
[3]Fengxian Central Hospital, Shanghai, China.

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Neuroplasticity is nervous system changes that occur in response to experience. Different individuals may have different neuroplasticity due to their different experiences. Even monozygotic twins may develop different neuroplasticity. Depression is a disorder of decreased neuroplasticity. Recent evidences suggest that antidepressants act by enhancing neuroplasticity, which allows environmental inputs to modify the neuronal networks to better fine tune the individual to the outside world. Meanwhile, there is a great individual difference of antidepressant response. So, it was concluded that variance of neuroplasticity in the depressant patients may play a role for individual difference of antidepressant efficacy.

Key words: Neuroplasticity, antidepressant, individual difference.

INTRODUCTION

Neuroplasticity is nervous system changes that occur in response to experience. This idea was first proposed in 1890 by William James in The Principles of Psychology, though it was largely neglected for more than half a century (Berlucchi and Buchtel, 2009). It is well known that the brain consists of neurons and glial cells which are interconnected and all areas of the brain are plastic even after childhood (Rakic, 2002). For example, environmental changes could alter behavior and cognition by modifying connections between existing neurons and via neurogenesis in the hippocampus and other parts of the brain, like the cerebellum (Bonfanti et al., 2008; Bonfanti and Ponti, 2008; Ponti et al., 2008). It is evidenced that substantial changes occur in the cortical processing area, and that these changes can profoundly alter the pattern of neuronal activation in response to experience (Hanggi et al., 2011; Kiebel et al., 2008; Schlegel et al., 2012).

According to the theory of neuroplasticity, experience actually changes both the brain's physical structure (anatomy) and functional organization (physiology). Neuroplasticity is of importance in depression and antidepressant treatment effects. Neuroscientists are presently engaged in a reconciliation of critical period studies demonstrating the immutability of the brain after development with the new findings on neuroplasticity, which reveal the mutability of both structural and functional aspects (Bakos et al., 2009; Farina et al., 2009; Goshen et al., 2009; Ilin and Richter-Levin, 2009; Kitanishi et al., 2009; Penn et al., 2009; Veyrac et al., 2009; Workman et al., 2009; Zhu et al., 2009). The paper discusses the potential role of neuroplasticity for difference of antidepressant efficacy.

DIFFERENT INDIVIDUALS MAY HAVE DIFFERENT NEUROPLASTICITY DUE TO THEIR DIFFERENT EXPERIENCES

The development of central nervous system is affected by coactions of both genetics and environment. Enriched environment significantly improve the brain growth and brain damage repair (Mundinano and Martinez-Millan, 2010)

*Corresponding author. E-mail: snownotrace@gmail.com or andrewfxu1998@gmail.com.

Prolonged stress can negatively impact capacity for neuroplasticity (Pittenger and Duman, 2008). A hypothesis was proposed that expression of neuroplasticity is a form of adaptation based on natural selection, where cells deprived of sensory input actively go and look for information in order to survive (De Ridder and Van de Heyning, 2007).

Different individuals have different degrees of neuroplasticity due to their different experiences (Zheng and Xu, 2012). It is widely accepted that environmental factor has an important role in this difference (Badenoch and Cox, 2010; Chung et al., 2009; Jarvenpaa et al., 2004; Siok et al., 2008). Furthermore, the estimated number of human protein-coding genes is around 35,000 (Ewing and Green, 2000). Meanwhile each hemisphere of human brain occupies about 10^{11} neurons, let alone the hundreds of connections that each neuron makes. This suggested that human genes contain too little information to specify neural system and there must be an important random factor in neural development (Zheng and Xu, 2012). Cortical laminar development shows a process that is mathematically consistent with a random walk with drift (Landing et al., 2002). Cerebral cortex has a range of interconnected functional architectures. Some exhibits random and without structure, while others are geometrical (Siegel and Read, 2001). Additionally, epigenetic factors have a role in neural development, which will lead to different expressions of a gene (Fraga et al., 2005). Thus, even monozygotic twins may develop different neural structure and neuroplasticity, though they share the identical gene background. These are evidenced by discordance in some diseases morbidity as the following examples. An investigation showed that significant hippocampal atrophy was detected in the demented twins when compared with the controls. Meanwhile, in the non-demented twins, non-significant reduction was observed in the hippocampal volumes compared with the controls (Jarvenpaa et al., 2004). Some monozygotic twins are discordant in many diseases such as bulimia nervosa (Bulik et al., 2001), schizophrenia (Cannon et al., 2000), bipolar disorders (Gourovitch et al., 1999), and sexual orientation (Hall and Love, 2003).

DEPRESSION IS A DISORDER OF DECREASED NEUROPLASTICITY

Various stress, such as bereavement, earthquake and disease (e.g. cancer), is a major environmental component for increased susceptibility to depression (Calabrese et al., 2011; Johansson et al., 2011; Liu et al., 2011; Morina et al., 2011). Depression is associated with a hyper-responsiveness to chronic stress (Hafner et al., 2011). Chronic stress, which can precipitate or exacerbate depression, decrease neuroplasticity, while antidepressant treatment produces opposing effects and can increase neuroplasticity.

Accumulating evidence demonstrates that neuroplasticity is decreased in depression. Though some researchers suggest that the complex biological and psychological changes associated with depression cannot be attributed to disturbance in hippocampal neurogenesis alone (Bessa et al., 2009; Tang et al., 2012), it is board acceptance that stress triggers activa-tion of the hypothalamic-pituitary-adrenal (HPA) axis, and causes the brain to be exposed to corticosteroids, affecting neurobehavioral functions with a strong downregulation of hippocampal neurogenesis, and is an important risk factor for depression (Kubesova et al., 2012; Masi and Brovedani, 2011; Santarelli et al., 2003). Early-onset depression and risk for depression are asso-ciated with decreased neuroplasticity (Lopez et al., 2010).

As important products of HPA axis, glucocorticoids are stress-induced steroid hormones (Numakawa et al., 2010), and increased glucocorticoid level is correlated with depression (Howell et al., 2011). Early life stress can program the development of the HPA axis, causing alterations of neurochemistry and signaling pathways related to neuroplasticity regulation, and then changing neurobehavior (Lai and Huang, 2011). Chronic or severe stress and high-dose treatment with glucocorticoids is surely decrease of hippocampal synaptic plasticity and morphological neuroplasticity. Prolonged stress can negatively impact hippocampal function and capacity for neuroplasticity. Various forms of acute and chronic stress and elevated levels of glucocorticoids have been shown to reduce hippocampus neurogenesis. Chronic restraint stress induces significant regression of the apical dendrites of pyramidal cells in medial prefrontal cortex (mPFC) and negatively impact mPFC function (Pittenger and Duman, 2008).

Stress and depression lead to atrophy of hippocampus. Glia loss and neuronal abnormalities have been observed in the prefrontal cortex in major depression. Noradrenergic axons have been found with reduced axonal arborization and density after stress exposure. Serotonergic axon sprouting seems to be dependent on brain-derived neurotrophic factor (BDNF), one of the neurotrophin family and a critical cytokine of neuroplasticity, which appears to be decreased after stress exposure. Therefore, it appears that stress and depression may increase neuronal atrophy degeneration. Additionally, hippocampal neurons continue proliferation well into adulthood. This continued neurogenesis relies on the presence of BDNF and serotonin and inhibited by glucocorticoids (Gould, 1999; Lee et al., 2002), both of which are altered in depression. Increasing evidence shows that antidepressant treatment may reverse the atrophy of hippocampal neurons, increase cell survival, and enhance monoamine axonal sprouting (Rush et al., 2004).

Cognitive function depends on hippocampal plasticity (Vanguilder et al., 2012). Recent data imply that hippocampus-specific deletions of BDNF in rodent models

induce cognitive deficits as well as impairment in extinction of aversive memory (Heldt et al., 2007). Accordingly, these animal model data are consistent with theory that decreased neuroplasticity within the hippocampus could contribute to depression. Particularly, these data suggest that hippocampal plasticity deficits contribute to both the cognitive deficits and the inability to decrease negative affective and cognition that are the characteristic of major depression.

Thus, alterations in neuronal populations in the depressed state likely contribute to the dysregulated affective neural circuitry. Reduced neuronal density and atrophy in the hippocampus and prefrontal cortex presumably contribute to decreased activity responsiveness. In addition, these processes likely serve to maintain a state of imbalance in depression by reducing the ability of cortical and hippocampal areas to inhibit or modulate the stress pathways of the amygdale and interconnected circuitry. The depressed state is the one in which these stress pathways cannot be easily returned to normal, and the individual is left in a chronic state of abnormal affective responsiveness.

ANTIDEPRESSANTS TARGET ON NEUROPLASTICITY

Clinical and basic researches demonstrate that chronic antidepressant treatment increases the rate of neurogenesis in the adult hippocampus. Antidepressants up-regulate cAMP and the neurotrophin signaling pathways involved in plasticity and survival. *In vitro* and *in vivo* data provide direct evidence that the transcription factor, cAMP response element-binding protein (CREB) and BDNF are key mediators of the therapeutic response to antidepressants. Depression maybe associated with a disruption of mechanisms that govern cell survival and neuroplasticity in the brain (D'Sa and Duman, 2002).

Emerging research in experimental animals changed the perception of researchers to understand stress as well as the effects of antidepressant agents. Recent findings from the basic neurosciences to the pathophysiology of depression suggest that stress and antidepressants have reciprocal actions on neuronal growth and vulnerability (mediated by the expression of neurotrophin) and synaptic plasticity (mediated by excitatory amino acid neurotransmission) in the hippocampus and other brain structures. Stress has the capacity to progressively disrupt both the activities of individual cells and the operating characteristics of networks of neurons, while antidepressant treatments act to reverse such injurious effects (Reid and Stewart, 2001). Antidepressants increase the expression of several molecules, which are associated with neuroplasticity, in particular BDNF and its receptor TrkB. Antidepressants also increase neurogenesis and synaptic numbers in several brain areas. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, can reactivate developmental-like neuroplasticity, which under appropriate environmental guidance, leads to the rewiring of a developmentally dysfunctional neural network (Balu et al., 2009; Guirado et al., 2009).

Antidepressants may act by enhancing neuroplasticity, which allows environmental inputs to modify the neuronal networks to better fine tune the individual to the outside world. Recent observations directly support this idea. According to the network hypothesis of depression, BDNF may act as critical tools in the process whereby environmental conditions guide neuronal networks to better adapt to the environment. Antidepressants may indirectly produce an antidepressant effect by increasing BDNF levels (Castren and Rantamaki, 2010).

INDIVIDUAL DIFFERENCE IN ANTIDEPRESSANT EFFICACY

Are antidepressants truly effective in all patients? Meta-analysis of all available trials of each antidepressant in the treatment of major depression, including treatment resistant depression and long-term relapse prevention is conducted by many researchers (Bauer et al., 2009; Kennedy et al., 2009; Rahimi et al., 2009). The efficacy and safety of antidepressants vary significantly. New evidences showed that the total effective rate of fluoxetine was about 77% (Duan et al., 2009). Various classes of antidepressant medications generally induce remission of major depression in only about one-third of patients. One double-blind study suggested the superiority of different combinations of antidepressants from treatment initiation. 105 patients meeting DSM-IV criteria for major depression were randomly assigned to receive, from treatment initiation, either fluoxetine monotherapy (20 mg/day) or mirtazapine (30 mg/day) in combination with fluoxetine (20 mg/day), venlafaxine (225 mg/day titrated in 14 days), or bupropion (150 mg/day) for 6 weeks. The primary outcome measure was the Hamilton Depression Rating Scale (HAM-D) score. The overall dropout rate was 15%, without notable differences among the four groups. Compared with fluoxetine monotherapy, all three combination groups had significantly greater improvements on the HAM-D. Remission rates (defined as a HAM-D score of 7 or less) were 25% for fluoxetine, 52% for mirtazapine plus fluoxetine, 58% for mirtazapine plus venlafaxine, and 46% for mirtazapine plus bupropion (Blier et al., 2010).

Although the use of antidepressants increased markedly during the 1990s, in recent years it has decreased as a result of concerns regarding the emergence of suicide during antidepressant treatment. There is evidence that SSRIs can improve adolescent depression better than placebo, although the magnitude of the antidepressant effect is 'small to moderate', because of a high placebo response, depending on the different

individual. A cautious and well-monitored use of antidepressant medications is a first-line treatment option in adolescents with moderate to severe depression. Low rates of remission with current treatment strategies indicate that further research in both psychotherapy and pharmacotherapy is warranted (Masi et al., 2010).

CONCLUSIONS

Why antidepressant efficacy varies among individuals? The degree of neuroplasticity is different in depressed patients. An individual difference in relation to antidepressant efficacy is identified. Neuropsychiatric disease treatment among individuals who have different nervous system structure and function may produce different efficacy (Zheng and Xu, 2012). So, neuroplasticity might be an answer to different antidepressants efficacy among individuals. Although, evidences for this hypothesis are needed to strengthen this important mechanistic links between antidepressant efficacy and neuroplasticity, it is suggested that the individual difference in neuroplasticity may play a role for individual difference in antidepressant treatment response. This hypothesis can be tested by comparing the antidepressant efficacy among different BDNF levels or anatomical structures. Furthermore, since the nervous system is the leading system in the human body, neuroplasticity may also play role in other disease treatment efficacy.

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