A Hypothesized Role for Dendritic Remodeling in the Etiology of Mood and Anxiety Disorders

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An elegant theory that links hippocampal neurogenesis to mood and anxiety disorders and to the mechanism of action of antidepressant drugs has gained widespread attention. However, depression and anxiety disorders involve multiple areas of the brain, such as the amygdala and prefrontal cortex, where neurogenesis does not appear to occur in the adult mammalian brain. A complementary theory is proposed here in which neurogenesis is seen as an epiphenomenon of a more widespread alteration in dendritic length and spine number. According to this theory, exposure to chronic stress and stressful life events increases excitotoxic glutamatergic neurotransmission in multiple brain areas. To protect neurons from consequent apoptosis, dendrites retract and spine number decreases, thus limiting the number of exposed glutamate receptors. Drugs that reduce glutamatergic neurotransmission under these circumstances, many of which have already been shown helpful in treating mood and anxiety disorders, may prevent this dendritic retraction and thus protect synaptic connections throughout the brain.

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A current and compelling theory for the etiology of depression and anxiety disorders involves decrease in brain neurotrophic factors and a consequent reduction in neurogenesis.[1–3] This theory has substantial experimental support from both preclinical and clinical studies. Included among the supporting data are the following points:

1. In animals, exposure to stress decreases expression of genes encoding and levels of brain-derived neurotrophic factor (BDNF),[4–6] its receptor (TrkB),[7] and molecules that turn on production of BDNF, including cAMP response element binding protein.[8]
2. Also in animals, stress causes a reduction in neurogenesis in the subgranular zone of the hippocampal dentate gyrus.[9,10]
3. Hippocampal neurogenesis is stimulated by all known antidepressant medications when given chronically but not acutely, and by known antidepressant and antianxiety treatments such as electroshock treatment (EST), thyroid hormone, and corticotropin releasing hormone (CRH)-1 antagonists.[11–14]

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4. Antidepressants block the ability of stress to reduce hippocampal neurogenesis.[15–17]
5. Interference with BDNF, TrkB receptors, cAMP response element binding protein, or neurogenesis in the hippocampus interferes with the ability of antidepressants to reduce fearful responses and hippocampal neurogenesis in experimental animals.[18]
6. Exposure to stressful life events and to chronic stress increases the risk for depression and anxiety disorders in humans,[19] particularly in genetically vulnerable individuals.[20]
7. Hippocampal volume is reduced in some, but not all, studies of patients with depression and anxiety disorders, suggesting a decrease in neurogenesis.[21,22]
8. BDNF levels are higher in postmortem brains from depressed patients who took antidepressants before death compared with those who did not.[23]

This impressive body of well-conducted studies nevertheless fails to account for several other important findings and aspects of depression and anxiety disorders as follows:

1. Although most published studies have shown relationships among BDNF, TrkB receptors, cAMP response element binding protein, and depression and/or antidepressant action, there are conflicting data.[24–30] These proteins are, of course, also involved in multiple crucial molecular events throughout the brain, so finding a relationship between them and depression does not automatically mean that this relationship is mediated through hippocampal neurogenesis.
2. Chronic stress produces dendritic remodeling in hippocampus but also in other brain regions including the amygdala and medial prefrontal cortex, areas that are not known to be capable of sustaining neurogenesis.[31–33]
3. The number of new neurons stimulated by antidepressant medication in the hippocampus is probably relatively small, and many of them may not mature to the point that they are capable of communicating either synaptically or electrically with other neurons.
4. Hippocampal neurogenesis may be important for the beneficial effects of antidepressant medication rather than for serving a major role in the pathophysiology of depression and anxiety disorder.[34]
5. The hippocampus is not the only region of the brain shown in neuroimaging studies to be involved in depression and anxiety disorders. There is abundant evidence for increased amygdala and decreased prefrontal cortex (PFC) activity as well.[35,36]

Perhaps most troubling for the neurogenesis theory in this regard is that current evidence suggests that neurogenesis may be restricted in the adult mammalian brain to the hippocampus and olfactory bulb.[37] Although evidence has emerged that neurogenesis may occur in other adult mammalian brain regions, including the neocortex and amygdala, this has been difficult to replicate.[38] It is, of course, plausible that the effects of neurogenesis within the hippocampus and olfactory bulb are transmitted to other parts of the brain through afferent pathways. The extensive connections between hippocampus and both amygdala and PFC might transduce the effects of neurogenesis, for example. However, so far no experimental evidence confirms that changes in neuronal number in the hippocampus that occur during stress or depression are sufficient to affect other areas of the brain. Hence, understanding how neurogenesis could be the key to a process like depression, which appears to involve multiple areas of the brain, is problematic. Therefore, it is reasonable to question whether hippocampal neurogenesis is sufficient to explain all aspects of disease processes as complex as anxiety and depression.

The last point is especially important when considering the role of neurogenesis in depression and anxiety disorders. The PFC is the most advanced part of the human brain in terms of differentiating it from our nearest genetic neighbors, the chimpanzee, bonobo, and gorilla, and enabling uniquely human mental and cognitive functions, such as complex thought, long-range planning, worrying about the distant future, altruism, and logic.[39] All of these are disturbed in patients with mood and anxiety disorders. While all animals are capable of showing fear and some nonhuman primate species manifest depression-like behavior during bereavement and a limited capacity for altruism and future planning,[40] none of these are nearly as complex as seen in humans. Indeed, there is no evidence that even chimpanzees are capable of the kinds of emotions seen in many humans suffering from mood and anxiety disorders such loss of self-esteem, catastrophic thoughts, worry about the distant future, fear of social disapprobation, and hopelessness. If it is accepted, therefore, that illnesses like major depression and generalized anxiety disorder are uniquely human, then it follows that the part of the CNS that has undergone unique

evolution and development in *Homo sapiens*, the prefrontal cortex, must be critically involved in their pathophysiology.[41] Unless neurogenesis is robust in the PFC, it is unlikely to be the only process involved in human psychiatric disturbance.

Dendritic Morphology in Multiple Brain Areas Responds To Stress

Given that the neurogenesis hypothesis for anxiety disorders and depression is supported by considerable evidence, but nevertheless appears insufficient on its own to explain these disorders, it is reasonable to consider additional neuronal factors. What other processes may also be involved in the brain of a depressed or pathologically anxious individual? The complementary hypothesis proposed here is that widespread dendritic remodeling in key regions of the CNS plays a key role in human mood and anxiety disorders. In the brain, dendrites are constantly expanding and contracting in length, often in an experience- or activity-dependent manner. On these dendrites, small projections called spines emerge or disappear. Spines express postsynaptic receptors for most neurotransmitters and seek out synaptic connections with boutons on axons of presynaptic neurons, again in an activity- and experience-dependent way.[42] Changes in the size and shape of the dendritic arbor and in the density of dendritic spines are central elements in activity-dependent synaptic plasticity.[43] A recent study, for example, showed that dendritic spine number is increased in the PFC of marmoset males who father young compared to those who are childless.[44] Many neurotrophic factors, including brain-derived neurotrophic factor (BDNF), have been shown to enhance dendritic arborization and increase dendritic spine number, thus increasing the number and strength of synaptic connections in the brain.[45] Dendrites have been shown to grow in a mature vertebrate cortex via active neuronal pathways.[46] Recent studies have also shown that dendritic spine shrinkage and enlargement are key components of two major molecular memory processes, long-term potentiation and long-term depression.[47–49]

It has been known for more than a decade that psychosocial stress causes atrophy of apical dendrites in the CA3 region of the hippocampus.[50] In preclinical studies in which animal models are used as replicas of human psychiatric illness, the response to experimental stress is often used as a proxy for the symptoms of anxiety disorders and depression. Given the current emphasis on the role of stress in the generation of anxiety and depression in humans (e.g., Kendler et al.[19]), it is reasonable to use such preclinical studies to consider the role of dendritic remodeling in these disorders. However, given that stress has been implicated in a number of other psychiatric disorders, it is also possible that the hypothesis proposed here applies more generally. During chronic stress, dendritic arborization, length, and spine number have all been shown to decrease in the PFC as well as the hippocampus.[32,51] Excessive excitatory neurotransmission supported by glutamatergic activation of NMDA receptors and diminished by GABA-ergic neurotransmission decreases dendritic length and spine number. Of note, Hashimoto et al.[52] reported increased glutamate levels in the frontal cortex of postmortem brains from patients with major depression and bipolar disorder. Similarly, the stress hormone corticotropin releasing factor (CRF), known to play an important role in anxiety and depression, adversely affects dendritic morphology during brain development[53,54] and causes rapid loss of dendritic spines after experimentally induced stress in laboratory animals.[55]

Thus, the complementary hypotheses to the neurogenesis theory are as follows:

1. Both acute traumatic stress and chronic stress decrease brain neurotrophic activity and increase glutamatergic neurotransmission and CRF signaling in multiple areas of the brain, including the hippocampus and prefrontal cortex.
2. Excessive stimulation of neurons has been shown to cause reduction in dendritic spine number.[56]
3. The decrease in spine number and retraction of dendrites, as well as internalization of NMDA receptors via the clathrin pathway,[57] are adaptive maneuvers to limit the number of exposed NMDA receptors and therefore decrease the opportunity for excessive excitatory neurotransmission to cause neuronal death. A similar suggestion has been made recently to explain the decrease in the number of prefrontal cortical dendritic spine synapses in an animal model of schizophrenia involving excessive release of glutamate.[58]
4. The consequence of these dendritic changes is fewer synaptic connections and a relatively "disconnected" brain. In a recent fMRI study, Liston et al.[51] showed

that chronic psychosocial stress in humans caused a reversible disruption in functional connectivity within a frontoparietal attentional network that the authors state

> can be easily understood within the framework of rodent studies showing alterations in dendritic arborization and axospinous inputs, which in turn may disrupt both local oscillatory activity with the PFC and long-range corticocortical connections between the PFC and more distant areas. . ."[51]

5. Antidepressant treatments inhibit glutamatergic neurotransmission and stimulate growth factor production, thus permitting dendritic expansion and "reconnection" of the brain.

The above hypothesis accounts for several features of both preclinical and clinical studies in depression and anxiety. First, it overcomes the problem of placing too much emphasis on changes in neurogenesis, which, while of great interest, are limited in scope and distribution throughout the adult mammalian brain.[59] Second, it retains the idea that chronic stress affects the expression of neurotrophic factors and that this is a key element in the etiology of these disorders. Third, it hints at a cause for the inability of depressed and anxious patients to use logic to diminish their out-of-control negative and catastrophic thoughts, their worries and fears, and their sense of hopelessness and helplessness. That is, with fewer synaptic connections, normal inhibitory functions of the PFC over the amygdala[60] are disrupted so that fear cannot be regulated, positive memories from the hippocampus cannot be recognized by the PFC, nor can negative memories be modified, and rational thinking is compromised. Of course, the data that form the foundation for this dendritic remodeling hypothesis are gleaned largely from preclinical studies, in the spirit of the current emphasis on "translational neuroscience." Therefore, the extrapolation to human psychiatric illness is only as solid as the validity of current animal models of fear, learning, and memory to the clinical arena.

The Dendritic Remodeling Hypothesis Has Therapeutic Implications for Depression and Anxiety Disorders

Finally, the theory proposed here would help to explain how antidepressants; glutamate antagonists; and positive environmental manipulations, including psychotherapy, can increase dendritic arborization and spine density in multiple relevant areas of the brain, leading to antistress and antidepressant effects. Deletion of the TrkB receptor, the receptor to which BDNF binds, has been shown to cause reduction in spine density in the CA1 region of the hippocampus.[61] Recently, Chen and colleagues[15] created a transgenic mouse with the same polymorphism in the gene encoding BDNF (Val66Met) that has been associated in humans with decreased hippocampal volume. Not only did the mice with the Val/Met mutation have reduced hippocampal volume and BDNF levels compared to wild-type mice, they also had decreased dendritic arbor complexity and a depressed-anxious phenotype. This suggests that research implicating BDNF as a target for antidepressant action may actually have disclosed a BDNF effect on dendritic morphology rather than on hippocampal neurogenesis. On the other hand, short-term treatment with fluoxetine increases dendritic spine and synapse formation in rat hippocampus.[62] Norrholm and Ouimet[63] similarly showed altered dendritic spine density in animal models of depression that responded to antidepressant treatment. Enriched environment caused an increased arborization of mossy fibers in mouse hippocampus in one study,[64] and in another,[65] enriched environment improved spatial learning and decreased anxiety-like behavior in mice even when the hippocampus had been irradiated and neurogenesis consequently blocked. The latter study again suggests that neurogenesis may not be necessary for antidepressant-like manipulations to work.

The clearest experimental evidence for the theory proposed here was recently provided by Bessa et al.[66] These investigators showed that blocking hippocampal neurogenesis in rats with the cytostatic agent methylazoxymethanol (MAM) did not prevent antidepressants with a range of mechanisms of action from reversing the depression-like behavior invoked by exposure to chronic mild stress. On the other hand, the antidepressants did reverse damage to dendrites and synaptic connections caused by stress exposure, both in the hippocampus and the PFC. These findings allowed the authors to conclude that it is more likely that antidepressants work by promoting dendritic remodeling rather than hippocampal neurogenesis.

Although stimulation of glutamate receptors is necessary for the normal development of the dendritic arbor,[67] the speculation here is that excessive glutamate

neurotransmission caused by exposure to stress is responsible for diminution of dendritic length and loss of spines. If antidepressant therapies promote dendritic remodeling, it could be argued that this would only expose them to the toxic effects of hyperactive glutamatergic neurotransmission and hence be counterproductive. Thus, it would appear critical that antidepressant therapies also reduce excessive glutamatergic release or block glutamate receptors, an idea long championed by Scolnick.[68] Preclinical evidence is emerging that this is the case.[69,70] Boyce-Rustay and Holmes[71] recently showed that inactivating the NR2A subunit of the NMDA receptor in genetically altered mice produced anxiolytic and antidepressant effects. In one study, fluoxetine and desipramine exerted moderate but selective effects while reboxetine, an antidepressant available outside of the United States that blocks norepinephrine reuptake, showed strong effects in decreasing glutamate receptor expression in both the hippocampus and PFC.[72] Riluzole, a drug that decreases glutamate neurotransmission, increased both BDNF and neurogenesis in the CA3 region of the rat hippocampus.[73] Johnson and Shekhar[74] showed that NMDA receptor antagonists blocked lactate-induced panic-like responses in their rodent model of panic disorder. Baskys et al.[75] showed that stimulation of group I metabotropic glutamate receptors, which decreases presynaptic release of glutamate via a negative feedback mechanism, reduces excitotoxic injury and promotes neurogenesis.

Clinically, drugs that inhibit glutamatergic neurotransmission, including lamotrigine, riluzole, metabotropic glutamate receptor agonists, memantine, and acamprosate, are in various stages of testing for their efficacy in mood and anxiety disorders. Mathew et al.[76] reported positive effects of riluzole in generalized anxiety disorder, and Zarate et al.[77,78] also reported efficacy for riluzole, which is marketed for the treatment of amyotrophic lateral sclerosis, in depression. Dramatic effects of the NMDA receptor blocking drug ketamine have also been reported in patients with depression.[79] Lamotrigine is a drug with multiple actions including decreasing glutamatergic neurotransmission and is already widely used for the treatment of bipolar disorder, for which it seems to have particularly strong efficacy for depression. The antibiotic ceftriaxone, which increases presynaptic glutamate reuptake, was found to have antidepressant properties in mice[80] and will surely be studied in human clinical trials in the very near future.

There is particular interest in the role that antidepressant drugs play at the level of the NR2B subunit of the NMDA receptor. Preclinical studies have shown that the NR2B subunit plays a critical role both in the development of dendritic arbor morphology[81] and in synaptic plasticity and learning.[82] The NR2B subunit has also been found to be central in the effect of acute stress on hippocampal long-term potentiation and depression of memory.[83] Burghardt et al.[84] found that chronic, but not acute, administration of the antidepressant citalopram decreased conditioned fear responses in association with down-regulation of the NR2B subunit of the NMDA receptor. The group found similar effects with acute administration of the glutamate blocking agent memantine, which is already marketed for the treatment of Alzheimer's disease.[85] An NR2B selective antagonist, Ro25-6981, exerted antidepressant effects in mice.[86] There is a report of another NR2B subunit specific NMDA antagonist, CP-101,606, having antidepressant effects in a placebo-controlled trial involving depressed patients.[87]

Therefore, there is clearly widespread interest in the possibility that blocking excessive glutamatergic neurotransmission may be an effective antidepressant and antianxiety maneuver. The speculation here is that this works by blocking the excitotoxic effects of excessive glutamate on dendrites in multiple brain areas, including prefrontal cortex and hippocampus, that are an integral part of exposure to repeated stressful life events and ultimately to mood and anxiety disorders. In addition, molecules that stabilize or increase dendritic branching could be candidate antidepressant and antianxiety drugs. For example, cypin, a protein that binds to the protein postsynaptic density-95 (PSD-95), was recently shown to promote the formation of stable dendritic branches.[88] Perhaps cypin, or a similar molecule, might have efficacy in human psychiatric illness. Other molecules recently discovered to promote dendritic spine protrusion are netrin-G ligand (NGL)[89] and synaptic adhesion-like molecule 2 (SALM2).[90] Also, a microRNA, miR-134, has recently been shown to be brain-specific and to regulate the size of dendritic spines.[91] There is currently great excitement that microRNAs may be involved in gene transcription patterns that are relevant to CNS disorders, and in this case a relationship to anxiety and depression is also a possibility. Finally, in keeping with current emphasis on the role of epigenetic factors in human psychiatric illness, it has been found that overexpression of histone deacetylase-2

(HDAC2) decreased spine density and memory formation.[92] An inhibitor of HDAC, vorinostat, is already approved for cancer therapy.

There are several aspects to the hypotheses proposed here that will require further clarification before they can be accepted. These include:

1. Changes in brain volume such as those observed in the hippocampus and amygdala are not specific to depression or anxiety disorders but have been reported in many psychiatric disorders including schizophrenia, autism, and bipolar disorder. Whether dendritic remodeling occurs in all of these conditions is as yet unclear, although it is fair to say that one thing all psychiatric disorders have in common is the experience of chronic stress.
2. If dendritic remodeling is a central feature of depression and anxiety disorders, and effective antidepressant medications reverse shrinkage in dendritic arborization and loss of dendritic spines, then it is not clear why only a subset of depressed and anxious patients respond to antidepressant medications. Clearly, dendritic remodeling secondary to exposure to environmental stress and induction of excitatory neurotransmission cannot be the only factors involved in the pathophysiology of these disorders, any more than neurogenesis can explain every aspect of complex disorders like depression. Several other factors, like intracellular signaling, may also be important. It is clear that genetic predisposition plays an important role in the vulnerability to the effects of stress and likelihood in developing depression or an anxiety disorder, and such congenital effects may also influence which patients respond to antidepressant therapy.
3. Changes in dendritic morphology can occur on a much faster time scale than that needed for either the maturation of new neurons in the adult hippocampus or the response to antidepressant therapy. So far, the decrease in dendritic length and spine number has been observed only in association with chronic stress,[33,51] and it remains to be seen whether the effects of stress and antidepressants on dendritic morphology are mediated by factors that require a longer than acute timeframe.

The theory proposed here can be tested experimentally in a number of ways. First, further studies documenting the effects of stress on neurotropin activity; glutamatergic neurotransmission; and dendritic length and spine number in areas outside of the hippocampus, particularly the PFC, should be done. Second, studies investigating whether standard antidepressant therapies block such stress-induced changes in PFC dendritic morphology are needed. These should be followed by preclinical experimental interventions such as the application of drugs that enhance neurotropin expression and/or reduce glutamatergic activity to the PFC during chronic stress to see if these too block dendritic retraction. Finally, further studies of "antiglutamatergic" drugs and of drugs that promote dendritic growth in patients with depression and anxiety disorders may demonstrate the clinical significance of the hypothesis. As noted above, although most emphasis has recently been placed on the role that stress has in the etiology of mood and anxiety disorders, to the extent that psychiatric illnesses in general are stress related, it is plausible that the dendritic remodeling hypothesis we have proposed will apply more generally across psychiatric diagnoses. As neuroimaging techniques that allow assessment of dendritic morphology in living human brain become available, it will be possible to test this hypothesis directly in clinical subjects. Until then, the usefulness of this hypothesis to clinical practice rests in its ability to predict therapeutic interventions, such as drugs that decrease glutamatergic neurotransmission or promote dendritic arborization, that are effective in treating mood and anxiety disorders.

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