Genetics of Childhood Disorders: XXXIX. Stem Cell Research, Part 3: Regulation of Neurogenesis by Stress and Antidepressant Treatment

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Mood disorders continue to be major medical problems that affect up to 17% of the population at some point in life and can result in loss of life. Although effective treatments exist, not all patients respond to available medications and there is a time lag of weeks to months in the therapeutic response to antidepressants. The pathophysiology underlying mood disorders has not been identified. Recent advances in neurobiology provide a new conceptual framework for investigating both the pathophysiology and the treatment of mood disorders. These studies demonstrate that regulation of brain function can occur via structural remodeling or synaptic plasticity of the cellular components of the brain. This includes neuro-

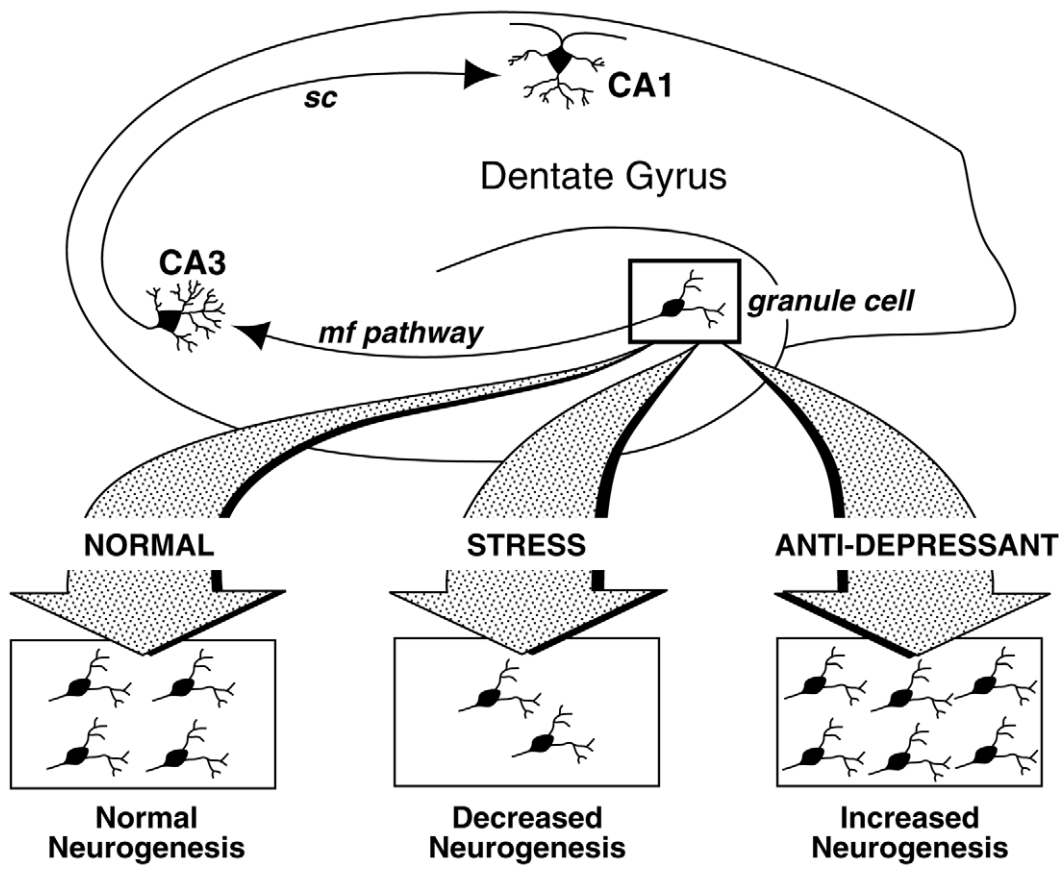

Fig. 1 Schematic model of hippocampus and regulation of adult neurogenesis. The major circuit in the hippocampus consists of granule cells in the dentate gyrus sending projections to the CA3 pyramidal neurons via the mossy fiber (mf) pathway, and CA3 neurons projecting to CA1 neurons via Schaffer collaterals (sc). Stress is reported to influence the cellular components of this pathway in the hippocampus of adult rodent or nonhuman primate. This includes down-regulation of adult neurogenesis by exposure to social or psychological stress. In addition, stress decreases the dendritic arborization of CA3 pyramidal neurons (not shown). These results demonstrate that stress can lead to structural alterations in the adult brain that could contribute to atrophy of hippocampus observed in clinical studies of patients with mood disorders. In contrast to the effects of stress, antidepressant administration increases neurogenesis in the hippocampus of the adult rodent. This effect could block or reverse the actions of stress on hippocampal atrophy.

genesis (addition of new neurons) in the adult brain. In this review, the concept of structural remodeling will be discussed and evidence that the pathophysiology and treatment of mood disorders may be influenced by structural remodeling, particularly neurogenesis, will be examined. Additional reviews of these topics are listed at the end of this article.

Over the past 30 years, there has been a revolution in our understanding of how the brain works and consequently in our studies of the pathophysiology of disorders of the brain. During this time we have discovered that communication between the different cellular components of the brain is controlled by a number of neurotransmitter systems. These neurotransmitter systems control neuronal activity by regulating complex intracellular signaling pathways and expression of specific genes. Elucidation of these extracellular and intracellular pathways has led to the widely accepted notion that major psychiatric illnesses result from disruption of these neurochemical pathways, and a tremendous effort has been placed on identification of these specific neurochemical alterations.

In addition to neurochemical control of the brain, more recent studies demonstrate that structural remodeling of the cellular components of the brain also controls communication between neurons. Structural remodeling, often referred to as neuronal plasticity, can occur in several different ways. This includes a change in the number or shape of dendritic spines, the primary location for synapse formation, as well as alterations in the number and length of dendritic branch points. Moreover, contrary to what used to be considered dogma, the total number of neurons in certain brain regions can be altered in the adult brain.

Until recently, it was thought that after the brain reached an adult stage the capacity for adding new neurons was lost. However, neurogenesis has now been demonstrated in the brains of a variety of different adult species, including bird, rodent, monkey, and human. New cells are derived from neural progenitor cells that are localized to a few restricted brain regions. One region is the subventricular zone that gives rise to cells that migrate to the olfactory system. The other is the subgranular zone in the hippocampus, where new cells are added that mature into granule neurons in the dentate gyrus of the hippocampus. The hippocampus is a limbic brain structure that plays a role in learning and memory and control of several vegetative processes. It is also a structure that has been implicated in mood disorders, including depression and posttraumatic stress disorder (PTSD).

New cells added to the hippocampus differentiate and mature into adult neurons within a period of several weeks. The cells display characteristics of adult neurons, including physiological properties of mature cells. Evidence that adult neurogenesis contributes to brain function has come mostly from correlative studies. For example, the rate of neurogenesis is increased by a variety of stimuli including exercise, hippocampal-dependent learning, and estrogen. This suggests that there is activity-dependent regulation of neurogenesis that increases the functional capacity of the hippocampus. This possibility is supported by a study demonstrating that chemical inhibition of neurogenesis in adult rodents blocks hippocampal-dependent learning, indicating that new neurons have a functional role in the adult brain. However, it is important to point out that the extent of neurogenesis in the adult human brain has not been determined and the functional relevance of this process in primates remains to be established.

Neuronal remodeling and neurogenesis provide additional mechanisms for regulation of neurotransmission in the brain. The mechanisms for control of remodeling and neurogenesis have not been fully identified, but they are likely to involve extracellular and intracellular pathways, thereby linking neurochemical and structural changes in the brain.

In contrast to the positive effects of exercise and learning, neurogenesis can also be regulated in a negative manner. This has been demonstrated most dramatically by exposure to stress, which results in a robust down-regulation of adult neurogenesis in the hippocampus of rodents and nonhuman primates (Fig. 1). Several different types of stress have been examined, including both physical and social stressors. One of the first reports demonstrated that exposure of a marmoset monkey to a resident animal in its home cage, referred to as intruder stress, decreases the rate of neurogenesis in the hippocampus of the intruder. Although this is considered a stressful condition for these very territorial animals, the time of exposure was very short (1 hour) and the two animals were never in physical contact because they were separated by a wire mesh. Similar effects have been observed in tree shrews with the resident–intruder stress model. Exposure to predator stress (e.g., fox odor) or foot shock is also reported to decrease neurogenesis in the hippocampus of adult rodents.

In addition to these types of stress, a recent study demonstrated that exposure of animals to a behavioral model of depression can decrease adult neurogenesis in the hippocampus. In this model, referred to as the learned helplessness model, animals are exposed to an inescapable stress condition that results in a state of "helplessness." That is, animals exposed to the inescapable stress are no longer capable of escaping upon subsequent testing even though escape is now possible, and administration of an antidepressant can reinstate the ability to escape. We have found that exposure to inescapable stress results in down-regulation of neurogenesis in the hippocampus that correlates with behavioral helplessness. Taken together, these studies demonstrate that different types of stress, including social, physical, and psychological stress, can decrease neurogenesis in the adult hippocampus.

The mechanism underlying the down-regulation of neurogenesis in the hippocampus by stress has not been fully characterized. Activation of the hypothalamic-pituitary-adrenal axis

clearly plays a role, however. Administration of a high dose of adrenal glucocorticoids similar to what would be observed under stressful conditions decreases the rate of neurogenesis in the adult hippocampus. A role for glucocorticoids in the regulation of neurogenesis has also been demonstrated in a study of neurogenesis in aging. Neurogenesis continues to occur in aged animals, although at a reduced rate. If the adrenal hormones are removed, the rate of neurogenesis returns to that seen in young animals. The results demonstrate that aging-induced elevation of glucocorticoids can account for the decreased rate of neurogenesis that is observed with age. The exact molecular and cellular mechanisms underlying the effect of glucocorticoids on neurogenesis are currently being studied and may involve regulation of excitatory amino acid neurotransmission.

In addition to decreased neurogenesis, repeated stress also alters the dendritic morphology of a major population of neurons in the hippocampus, termed CA3 pyramidal cells (see Fig. 1). McEwen and colleagues have found that exposure to restraint stress for 2 weeks decreases the dendritic arborization of CA3 neurons. This includes a decrease in the number and length of the apical dendrites. Combined with a reduction in neurogenesis of granule cells, the atrophy of CA3 neurons could result in a significant reduction in the function of the hippocampus.

These studies clearly demonstrate that stress can negatively regulate neurogenesis and cause neuronal atrophy in the adult hippocampus. However, there is little or no information on how stress influences neurogenesis and dendritic morphology in a developing brain. Given the high degree of stress that children and adolescents may be exposed to and the increasing awareness of psychiatric disorders in these age groups, it will be important to investigate this relationship in future studies.

Stress is known to play a major role in mood disorders, often being involved in either the precipitation or worsening of depression as well as other illnesses. On the basis of preclinical studies demonstrating that stress can reduce neurogenesis and can cause atrophy of neurons in the hippocampus, clinical investigators began asking whether structural alterations might be found in the brains of patients with illnesses related to stress. Magnetic resonance spectroscopy imaging studies demonstrate that the volume of the hippocampus is significantly decreased in patients with depression or PTSD. Several independent investigators have confirmed these findings in different patient populations. These findings raise the possibility that a reduction in hippocampal volume, as well as hippocampal function, contributes to the cognitive and vegetative abnormalities observed in depressed patients.

The reduction in hippocampal volume has been shown to correlate directly with the duration of depressive illness, but not the age of the individual. This suggests that depression may cause a reduction in hippocampal volume, and not that decreased volume leads to depression. However, it is possible that small changes in hippocampal volume contribute to the formation of depression and there is then a continued progression of the volumetric change. This could result from continued stress associated with illness. Additional studies will be needed to determine whether decreased hippocampal volume is a trait or state marker. It will also be important to determine whether the effect is reversible with antidepressant treatment.

The exact role of neurogenesis in depression and reduction in hippocampal volume has not been determined. It is conceivable that down-regulation of neurogenesis in the adult brain could contribute to a decrease in hippocampal volume. It has been calculated that neurogenesis adds up to 250,000 new cells per month in the rodent hippocampus, or 6% of the total number of existing granule cells. Although the numbers in both nonhuman primates and humans are much lower, it is possible that inhibition of this process could contribute to a reduction in the overall volume of the hippocampus. It is likely that atrophy of CA3 pyramidal neurons as well as other cell types could contribute to the overall reduction in the size of this brain region. Additional postmortem studies will be required to determine fully the cellular mechanisms that account for decreased hippocampal volume in mood disorders.

In addition to the changes observed in the hippocampus, recent studies also demonstrate structural alterations in the cerebral cortex of patients with mood disorders. Brain imaging studies demonstrate that the volume of the subgenual prefrontal cortex is decreased in patients with depression or bipolar disorder. Moreover, postmortem studies of patients with these illnesses also find that the number and size of neurons and glia are decreased in the cerebral cortex. Although reduced neurogenesis does not appear to account for these cortical changes, these results demonstrate that atrophy and cell loss in mood disorders are not restricted to the hippocampus. Further studies will be needed to determine the cellular mechanisms underlying the cerebral cortical changes observed in depression and bipolar disorder.

We have also been interested in identifying the molecular and cellular mechanisms underlying the actions of antidepressants. Toward this goal, we found that antidepressant treatment increases the expression of brain-derived neurotrophic factor (BDNF), a major neurotrophin in the brain. This discovery, combined with reports that stress causes atrophy and cell loss in the hippocampus, leads to the notion that neurotrophic actions could contribute to the effects of antidepressants. To examine this possibility, we studied the influence of antidepressant treatment on neurogenesis in the adult hippocampus. We found that administration of different classes of antidepressants, including norepinephrine and selective serotonin reuptake inhibitors, up-regulates neurogenesis in the hippocampus of adult rodents. Increased neurogenesis was dependent on several weeks of antidepressant administration consistent with the time course for the therapeutic action of antidepressants. In addition, up-regulation of neurogenesis was not

observed with other classes of psychotropic drugs, demonstrating a pharmacological specificity for antidepressants. Several different investigators have now reported that both chemical antidepressants and electroconvulsive seizures increase neurogenesis in the adult rodent hippocampus.

In addition to studies in normal animals, the influence of antidepressant treatment on the down-regulation of neurogenesis in rodents exposed to learned helplessness has also been examined. As described above, learned helplessness is a behavioral model of depression. We have found that helplessness in this paradigm is associated with decreased neurogenesis. We have also found that antidepressant treatment blocks the down-regulation of neurogenesis and reverses the behavioral helplessness in this paradigm. Additional studies are being designed to test directly the role of neurogenesis in the behavioral responses observed in the learned helplessness model. However, the results suggest that up-regulation of neurogenesis could contribute to behavioral alterations in this model. Moreover, increased neurogenesis would be expected to oppose the actions of stress on the hippocampus and could help to reverse or block the atrophy of the hippocampus observed in patients with mood disorders.

The results discussed in this column highlight significant conceptual advances for understanding the pathophysiology and treatment of mood disorders. These include the astonishing discoveries that the shape and number of neurons can be altered in the adult brain. Moreover, structural, as well as neurochemical, alterations have been observed in the brains of patients with mood disorders, and antidepressant treatment could oppose these structural changes. Taken together, these findings raise the possibility that novel therapeutic interventions targeted at neuronal number and morphology can be developed with the hope of more efficacious and faster-acting drugs. It is also interesting to speculate that behavioral therapy could be designed to enhance the effects of antidepressants. For example, exercise and learning are reported to increase neurogenesis in the adult brain, and it is possible that a combination of drug and behavioral therapy could produce a greater therapeutic response. This possibility is supported by clinical studies demonstrating that exercise can produce antidepressant effects in depressed individuals. The continued use of state-of-the-art neurobiological studies holds a bright future for the development of better treatments, and possibly the prevention, of mood disorders.

WEB SITES OF INTEREST

http://info.med.yale.edu/chldstdy/plomdevelop/development/december.html
http://info.med.yale.edu/chldstdy/plomdevelop/development/January99.html
http://info.med.yale.edu/chldstdy/plomdevelop/development/February99.html

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