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Neuroplasticity: from MRI to depressive symptoms

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Abstract

Morphological and functional changes have been repeatedly reported in the brain organization of depressed patients. The main modifications demonstrated by structural magnetic resonance imaging (MRI) are a reduction in the gray matter volume within the prefrontal cortex, the hippocampus, and the striatum. The reduction in gray matter volume and the morphological atrophy are probably due to an excess of neural loss (apoptosis) and an altered regulation of the neurotrophic processes. Hence, a deficit in neurotrophic factor synthesis (brain-derived neurotrophic factor [BDNF], neurotrophin [NT]-3, NT-4/5, Bcl-2, etc.) may be responsible for increased apoptosis in the hippocampus and prefrontal cortex corresponding to the cognitive impairment described in depression. This hypothesis seems to be confirmed by the decreased expression of neurotrophic factors (e.g., BDNF mRNA) in animal models of depression. In parallel, the neural plasticity (functional aspects of synaptic connectivity and long-term potential activity [LTP]) is decreased. However, the most interesting data concern the possible reversibility of this dysregulation with antidepressant treatment. For example, communication between the hippocampus and the prefrontal cortex could be re-established, enabling in a way the cognitive processes to be "reset." From a clinical point of view, the consequences of such a phenomenon are manifold:

- apoptosis and neurotrophic deficits could explain most of the symptoms of depression depending on the regions concerned;
- the resulting alterations in neuroplasticity could explain the dysconnectivity found between the same regions;
- enhancing neurotrophic synthesis in those regions could not only stimulate synaptogenesis and reverse neural (dendritic) atrophy but could also play a positive role in LTP genesis which is crucial for re-establishing adapted communication.

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1. Introduction

The brain is now considered to be an open, selfpreserving, dynamic system that derives its structural and functional capacity from the interaction of genes and environmental factors. Fundamental interdependent cascades of processes maintain neuronal survival throughout brain development and the life span. The term "neuroplasticity" subsumes these cascades of processes that allow the brain to constantly adapt to internal and external demands.

Evidence linking stressful life events and depression and findings from neuroimaging and postmortem studies suggest that mood disorders may be associated with impairment in processes involved in structural plasticity within specific neural networks. From this perspective, depression may result not only from changes in neurotransmitter concentrations and receptor activity levels, but also from impairment of the ability to make appropriate neuronal adaptations, synaptic connections, and neurogenesis. This "neurotoxic hypothesis" of mood disorder is reinforced by preclinical studies showing that molecules critical for neurotrophic cascades and neuronal viability are the main targets of antidepressant drugs.

2. Cerebral changes and neurotoxic hypothesis of depression

Among the variety of approaches that have been used to study the pathophysiology of mood disorders and target

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antidepressant drugs, important data come from tissue studies (peripheral cells from patients before and after drug treatment and postmortem brain studies) and brain imaging studies, including positron emission tomography and magnetic resonance imaging (MRI).

Findings from these approaches suggest that depression may be associated with impairment of structural and functional plasticity and cellular resilience within a specific neuronal network composed of prefrontal cortex (dorsolateral, medial, and orbital regions), cingulate and paracingulate cortex, amygdala, and hippocampus (Manji et al., 2003). These findings also suggest that the recurrence of depressive episodes may enhance the deleterious effect of depression on structural and functional plasticity of these circuits, the so-called "neurotoxic hypothesis" of depression.

This hypothesis implies demonstration of (1) impairment in the cascades of processes involved in neuroplasticity in patients with depression; (2) greater impairment in patients with recurrent depression than patients with a single episode; and (3) a relationship between the number of depressive episodes (or the duration of illness) and the structural and functional abnormalities reflecting impaired neuronal plasticity. To our knowledge, only preliminary evidence supports this hypothesis for both structural (see Sapolsky, 2000a) and functional (see Fossati et al., 2004) levels.

2.1. Postmortem studies in depression

Postmortem studies in patients with depression indicate a reduction in neuronal size in the orbitofrontal cortex, a reduction in glial number and size in the prefrontal and orbitofrontal cortex, and a decrease in cortical thickness and basal ganglia volume in patients with depression (Manji et al., 2001; Ongur et al., 1998; Rajkowska, 2000a,b). Cell number may also be increased in the hypothalamus, which may be relevant to the prominent neurovegetative symptoms of these disorders.

A loss of glia is the best replicated finding (Rajkowska, 2000a), affecting orbital and medial prefrontal cortex, as well as several subdivisions of the anterior cingulate (subgenual, pregenual). Glial abnormalities are seen in both bipolar and unipolar disorder and a decrease in glial density appears unique to mood disorders (Rajkowska, 2000b). Synaptic terminal and dendritic abnormalities, in support of aberrant cellular plasticity or impaired neurodevelopment, are also reported but appear to be a more selective marker of bipolar disorder. Despite repeated demonstration of hippocampal atrophy on MRI (see below), it remains to be determined whether there are changes in hippocampal cell number in subjects with mood disorders and decreased hippocampal neurogenesis as demonstrated in animal models of depression (Czeh et al., 2001).

It is unknown whether the glial and neuronal pathologies reported in postmortem studies of depressed patients are related to the pathogenesis of depression. Glial cells support many functions and are active partners in neuronal transmission. The reduced number of glial cells may be involved in neuroimaging reports of reduced glucose metabolism in the prefrontal cortex of depressed patients (Tsacopoulos and Magistretti, 1996). Taken together, these morphometric data may denote differences in neural connectivity in mood disorders.

2.2. Imaging studies in depression

Brain imaging studies have provided a vast amount of information about the neuroanatomic correlates of depression. Change in either size or function of prefrontal cortex, hippocampus, and amygdala is consistently reported in studies of subjects with these disorders (Campbell et al., 2004; Mayberg and Fossati, in press; Bench et al., 1995). Particularly, the works of Sheline et al. (1996, 2003) showed (a) reduced hippocampal volume in depressed patients, (b) a correlation with the duration of depression, and (c) volume loss and recovery of volume after antidepressant treatment. They also found that atrophy of the hippocampus in major depression worsens with repeated episodes. This could suggest that the hippocampal atrophy is the result of the illness rather than the etiological factors of depression.

The association between brain changes and the occurrence of depression has been studied using animal models. In animals, depression is represented by repeated stress paradigms; these paradigms have been shown to be reliable models of depression in rodents (Willner, 1984) as well as in tree shrews, a prosimian species model for studying the pathophysiology of depression (Fuchs et al., 1996). In this latter model of depression, as in patients, reduced total hippocampal volume has been observed (Czeh et al., 2001).

Furthermore, in these models two other structural modifications were observed:

- Atrophy (reduced number and length of apical dendrite branching) of the dendrites of the CA3 region (Magarinos et al., 1996).
- Decreased adult neurogenesis in the dentate gyrus (Gould and Tanapat, 1997).

2.3. Neuroplasticity and neurotrophic factors

Activity-dependent synaptic modifications, changes in postsynaptic cell excitability, cortical map reorganization (promoted by neurotransmitters and their receptors), and extension of specialized areas secondary to neurological disease or learning probably represent the most characteristic consequences of brain plasticity.

Plasticity of the central nervous system has been extensively studied during development. The famous visual deprivation studies of Wiesel and Hubel (1963) have shown that monocular deprivation during a critical period of early development in cats and monkeys results in loss of effective connection from that eye to the cortex. The remarkable recovery of motor function and language in children who have undergone hemispherectomy for untreatable epilepsy represents the most illustrative example of brain plasticity and its correlation to recovery from neurological insult.

Neuronal plasticity in the adult brain is manifested at the cellular level by modification of dendritic growth, axonal sprouting, synaptic remodeling, and creation of new synapses and is closely linked with neurogenesis (Mesulam, 1999).

Among these neuroplastic events, synaptic remodeling and synaptogenesis are largely influenced by neurotrophic factors, a group of proteins (neurotrophins) including nerve growth factor (NGF) and BDNF (brain-derived neurotrophic factor) (Patapoutian and Reichardt, 2001). BDNF is a major physiological survival factor that has been involved in several pathophysiological conditions, including mood disorders (Angelucci et al., 2004). BDNF exerts its neurotrophic action and neuroprotective effect through a cascade composed of Trk (tyrosine kinase) receptors, the MAP (mitogen-activated protein) kinase signaling pathway, and activation of bcl-2 expression. bcl-2 is an antiapoptotic protein regulating the cell death program (apoptosis) in order to control the final numbers of neurons and glial cells in the central and peripheral nervous systems. Apoptosis plays an important role in the cell death observed in acute and chronic neurodegenerative diseases. In contrast to necrosis, apoptosis is programmed and critically controlled by the levels of proapoptotic (BAX, BAD) and antiapoptotic (bcl-2 and bcl-xL) proteins within the cell (Yuan and Yankner, 2000).

Therefore, BDNF may provide the necessary trophic support for cell survival, but its neuroprotective effect may be mainly explained through an inhibition of cell death cascades.

2.4. Neuroplasticity and stress

In the dentate gyrus and the CA1 and CA3 regions of the hippocampus, stress and corticosterone treatment both decrease the expression of BDNF mRNA whereas they increase mRNA levels of the BDNF receptor, the catalytic TrkB (Nibuya et al., 1999; Scaccianoce et al., 2003). BDNF administration reverses learned-helplessness behaviors in a swim test paradigm (Duman et al., 1999), suggesting a link between stress, depressed-like behaviors, and BDNF.

Although the changes in the hippocampus may not alone explain the affective symptoms of depression, they provide a cellular basis for understanding the structural impairment observed in this brain region as well as in other regions associated with depression (see below). The proposed mechanism of stress-induced BDNF downregulation is repression of transcription of the BDNF gene promoter by the activated corticosteroid receptor (Schaaf et al., 2000). Dysfunction of the cAMP (cyclic adenosine monophosphate)/CREB (cAMP response element binding) signaling cascade might underlie the stress-induced BDNF downregulation (Dowlatshahi et al., 1998).

Moreover, recent findings suggest that increasing bcl-2 expression may protect against the neuronal consequences of severe stress (ischemia, stroke). Taken together, these data suggest that drugs that manipulate BDNF and bcl-2 expression have considerable value in the treatment of disorders linked to stress and impairment in the balance between cell survival/cell death such as mood disorders (Tsai, 2004).

Goggi et al. (2002) emphasized that BDNF also has an acute effect on the electrophysiological expression of synaptic plasticity (long-term potentiation [LTP]) and on neurotransmitter release by facilitating release of glutamate, gamma-aminobutyric acid (GABA), dopamine, and serotonin. BDNF may therefore exert short-term as well as longterm effects in order to promote neurotrophic and neurochemical support in strategic neural networks.

2.5. Neuroplasticity and neurogenesis

Adult neurogenesis is a significant phenomenon that will certainly provide answers to a wide array of previously intractable problems and offer a possible key to understanding and treating neuropsychiatric disorders such as depression, Alzheimer's disease, and schizophrenia (Arango et al., 2001).

Adult neurogenesis has now been generally accepted and has been found in the subventricular zone and dentate gyrus part of the hippocampus in the brains of adult mammals: rodents, tree shrews, marmoset monkeys, macaque monkeys, and humans (Eriksson et al., 1998; Gould and Tanapat, 1997; Gould et al., 1999a,b; Kornack and Rakic, 2001). New neurons appear to arise from progenitor cells in the hilus or subgranular zone of the dentate gyrus and to migrate to the granule cell layer where they differentiate into neurons (Kuhn et al., 1996). New neurons, because they are structurally plastic, are temporarily immature and highly susceptible to changes in the environment and to different life experiences. This might explain the apparent transient nature of most adult-generated cells. New hippocampal cells may integrate into the neuronal circuitry of hippocampus and may play a role in certain learning and memory functions (Barnea and Nottebohm, 1994; Gross, 2000). Thus, young granule cells in the adult dentate gyrus appear to exhibit robust LTP that, in contrast to mature granule cells, cannot be inhibited by GABA (Snyder et al., 2001).

New cells with neuron characteristics were also found in the neocortex of adult rats and macaques (Gould et al., 1999b; Rietze et al., 2000). Moreover, neurogenesis has been demonstrated in several additional brain regions in response to injury (Arvidsson et al., 2002; Gould and Tanapat, 1997; Magavi et al., 2000; Nakatomi et al., 2002). In monkeys, adult-generated cells were found in prefrontal cortex, temporal cortex, and parietal cortex. The density of adult-generated cells with neuron characteristics is much lower in cortical areas than in the dentate gyrus. These adult-generated neocortex cells may have several possible origins: (1) from the subventricular zone, the source of new olfactory bulb neurons in the adult rodent and monkey (Luskin, 1993; Kornack and Rakic, 2001); (2) from the local division of progenitors or from progenitors in the white matter (Gould et al., 2001).

Although recent estimates suggest that the number of new neurons produced in adulthood is much greater than was initially thought, the rate of neurogenesis in adulthood is still low when compared with the rate of neurogenesis during development. With regard to difficulties in detecting adult neurogenesis in laboratory animals, several studies have now shown that enriched environment living enhances the survival of newly generated cells, particularly in the hippocampus (Barnea and Nottebohm, 1994; Kempermann et al., 1997, 2002). Animals living in standard laboratory conditions lose more new cells than those living in relatively complex environments, and the relatively impoverished artificial environments may account for the detection of low numbers of new neurons in some regions or the inability to find new neurons in some areas. Likewise, learning and running have been shown to increase the number of new neurons in the hippocampus (Gould et al., 1999a; Lemaire et al., 2000) and to improve performance on hippocampusdependent tasks (Van Praag et al., 1999). Finally, a short-day photoperiod enhances the number of proliferating cells in the dentate gyrus, cingulate cortex, and hypothalamus of male hamsters (Huang et al., 1998).

Experience or activity exerts not only an acute but also a sustained effect on brain plasticity. Thus, in adult mice, a sustained effect on brain plasticity occurred in the context of significant improvements in learning parameters, exploratory behavior, and locomotor activity. An enriched living environment also decreased nonspecific age-dependent degeneration in mice, even though this stimulation started only in middle age (Kempermann et al., 2002).

Manipulation of the social environment (experience with a male for 2 days) results in stimulus- and sitespecific effects on the newly proliferated cells in the adult female prairie vole brain in comparison to social isolation. This general pattern persists 3 weeks later, indicating that social environment also exerts long-term effects on the newly proliferated cells. Social environment appears to act on cell proliferation, rather than cell death and many newly proliferated cells display a neuron phenotype (Fowler et al., 2002).

Taken together, these data suggest that treatment that facilitates and maintains cognitive and physical activities (i.e., behavioral therapy, cognitive rehabilitation) may promote neurogenesis and may be used as a target in the treatment of disorders—such as chronic depression and schizophrenia—characterized by reduced level of activities and social deprivation.

Exposure to stressful experiences decreases the numbers of new neurons in the dentate gyrus by downregulating cell proliferation of granule cell precursors (Gould and Tanapat, 1997). This effect appears to be region-specific. The stress-induced decrease in granule cell genesis is not just an adult phenomenon. Exposure of rat pups to aversive stimuli decreases the number of proliferating cells in the dentate gyrus during the first week of life (Tanapat et al., 1998).

Developmental stress in rats can permanently alter both young and adult neurogenesis by disrupting the proliferation of granule cell precursors in relation to alterations in the function of the hypothalamic-pituitary-adrenal (HPA) axis (Lemaire et al., 2000). Stress-induced glucocorticoid release and treatment with corticosterone-the primary glucocorticoid in rats-seems to be at least one of the presumed ways of inhibiting granule cell genesis, while normalizing glucocorticoid levels (by adrenalectomy and low-dose replacement) prevents this inhibition (Tanapat et al., 2001) and increases the proliferation of granule cell precursors and, ultimately, the production of immature granule neurons (Cameron and Gould, 1994). Glucocorticoid-induced inhibition of cell proliferation may occur not only during stressful experiences, but also across the life span. During the early postnatal period, rats undergo a stress hyporesponsive period during which levels of circulating glucocorticoids are low and relatively resistant to increase under conditions of stress (Sapolsky and Meaney, 1988). This period is associated with maximal neurogenesis in the dentate gyrus (Schlessinger et al., 1975). New cells in the dentate gyrus may play a role in hippocampal modulation of the response to stress (Herman et al., 1989). In aged animals, glucocorticoid levels naturally rise coincidentally with a decrease in the number of newly generated cells (Seki and Arai, 1995; Kuhn et al., 1996).

The role of glucocorticoids and stress in the modulation of neurogenesis in hippocampus has re-invigorated research on the link between stress, hippocampus, and mood disorders. It is well-known that depression may impair the function of the HPA axis with HPA activation associated with depression more likely linked to hippocampal volume reduction (Sheline et al., 1996; Boyer, 2000; Sapolsky, 2000b).

In contrast, ovarian steroids have a stimulatory effect on the proliferation of granule cell precursors. Ovarian steroids increase proliferation of granule cell precursors in the dentate gyrus (Ormerod and Galea, 2001). The rate of cell proliferation in the dentate gyrus fluctuates in association with breeding season in female meadow voles (Galea and McEwen, 1999), and this effect may be attributable to changes in estrogen levels across seasons (Ormerod and Galea, 2001). In addition to having a beneficial effect on cognition, estrogen by modulating neurogenesis in hippocampus may be of therapeutic value in stress-related disorders.

2.6. Alterations of neuroplasticity and symptoms of depression

These results have given rise to a new emerging hypothesis of the pathophysiology of depression which involves the plasticity of neural systems.

Depression is thought to result from an inability to make the appropriate adaptive responses to environmental stimuli due to the alteration in neuroplasticity: atrophy and loss of neurons and glia in the brain, which leads to structural as well as neurochemical alterations.

This hypothesis built on recent results (functional MRI, postmostem histology) allows the integration of previous findings (neurotransmitter alteration, HPA axis dysfunction) in the pathophysiology of depression. This hypothesis can be reinforced by evaluating the effect of antidepressant medication in the changes in brain plasticity.

The link between the alterations of neuroplasticity and depressive symptoms remains to be established. Since the hippocampus is one the main structures implicated in memory processes, it is possible that changes in hippocampal plasticity could be responsible for the memory deficits that are usually observed in depression. Madsen et al. (2003) have reported that inhibition of hippocampal neurogenesis is associated with memory impairments.

The structural changes reported in the amygdala of depressed patients (Frodl et al., 2003) could explain not only the anxiety symptoms frequently associated with depressed mood but also the aggressive behavior observed particularly in depressed adolescents.

It was believed that the effects of antidepressants were limited to the alleviation of depressive symptoms. Nevertheless, clinical practice has shown that, to avoid relapse, depressed patients should be treated months beyond clinical remission. This observation suggests that the action of antidepressants goes beyond simply the alleviation of clinical symptoms. The recent findings showing that antidepressant treatment regulates alterations in brain plasticity could explain the need for a long-term treatment. The improvement in neuroplasticity by antidepressants seems, therefore, to be of great interest, as it provides a rationale for the efficacy in the prevention of depressive relapse.

3. Neuroprotective effects of antidepressants

Although antidepressant drugs have been used for decades, the neurobiological substrate of their efficacy is poorly understood. Recently, it has been proposed that antidepressants may exert their long-term therapeutic effects by triggering cellular mechanisms that promote neuronal plasticity (Manji et al., 2003). Actions on neurotrophic

factors and neurogenesis support these neuroprotective effects of antidepressants.

3.1. Antidepressant and neurotrophic factors

Antidepressant treatment increases levels of serotonin and norepinephrine at the synapse, resulting in the activation of intracellular signal transduction cascades that couple to monoaminergic receptors.

BDNF and CREB are the main targets of these postreceptor cascades. Thus, chronic antidepressant administration increases the expression of CREB in rat hippocampus (Duman, 2000). The mechanism underlying the upregulation of CREB by antidepressants and by activation of monoaminergic systems has been characterized in vitro and in vivo. In vitro, CREB can be activated directly by the cAMP-protein kinase A (PKA) pathway via stimulation of norepinephrine (β -adrenergic and α -adrenergic) (Roseboom and Klein, 1995) and 5-hydroxytryptamine $(5-HT_{4,7})$ receptors (Duman, 1998). CREB activity can also be directly induced by Ca2+-dependent protein kinases and PKC, which are activated by stimulation of the adrenergic receptor and 5-HT₂ receptors (Duman, 1998). Finally, CREB can also be directly phosphorylated by activating the Ras-MAPK signaling pathway (Ghosh et al., 1994). This could explain, in part, how antidepressants that act by inhibiting norepinephrine and 5-hydroxytryptamine reuptake could mediate their effects on CREB.

CREB activation and phosphorylation by kinase promote BDNF gene expression and this upregulation of BDNF is dependent on chronic treatment, a finding consistent with the delay of clinical response to antidepressant. As recently demonstrated with several antidepressants and with electroconvulsive seizures (ECS), the cAMP/CREB/BDNF cascade was found to be upregulated by antidepressant treatments (Nibuya et al., 1995, 1996).

The neuroprotective effect of antidepressants may also be related to the increase in neuronal defence and the blockade of stress-induced atrophy of hippocampus CA3 neurons. The results of Czeh et al. (2001) support this hypothesis by demonstrating that chronic treatment with the antidepressant tianeptine reverses the stress-induced changes in metabolite concentrations, decreases in neurogenesis, and reduction in volume in hippocampus.

3.2. Antidepressants and neurogenesis

Antidepressants may target neuroprotective pathways by increasing the neurogenesis in hippocampus. Indeed, longterm antidepressant treatment and ECS can also increase the proliferation and survival of new neurons (Malberg et al., 2000). The results of Santarelli et al. (2003) suggest that an increase in hippocampal neurogenesis is necessary for the antidepressant action. Activation of the cAMP pathway or incubation with BDNF is reported to increase neuronal differentiation and neurite outgrowth of progenitor cells in vitro (Palmer et al., 1997). Studies are currently under way to examine the role of CREB and BDNF, as well as other factors, in the upregulation of cell proliferation in response to antidepressant treatment.

Finally, evidence that neurogenesis occurs in cerebral cortex suggests that the neurogenesis in these cortical regions might also be targeted by antidepressant treatment (Gould et al., 1999a,b).

4. Conclusion

Increasing evidence suggests that mood disorders, especially depression, may result from impairment in neuroplasticity and neuronal survival processes within a corticallimbic network. Antidepressant drugs may restore functional as well as structural plasticity within this brain circuitry. The evidence reviewed suggests that antidepressants, in order to exert these functional and structural actions, must be prescribed for a long-term period, consistent with the episodic and chronic nature of depressive disorders. The specificity of these neuroprotective effects of antidepressants remained to be determined as recent findings showed that mood stabilizers enhance neurotrophic factors (Bijur et al., 2000; Chen and Chuang, 1999) and increase neurogenesis (Chen et al., 1999; Wang et al., 1999). Likewise, further clinical and experimental in vivo and in vitro studies are needed to determine genetic and environmental factors that regulate structural and functional plasticity within the neural network regulating mood and affective behavior and to prepare the ground for the development of novel antidepressant treatments.

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