The neurobiology of treatment response to antidepressants and mood stabilizing medications

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As the neurobiology of mood disorders and the mechanisms of action of antidepressant drugs continue to be elucidated, there has been a shift in emphasis from changes in neurotransmitter release and metabolism to regulation of gene expression and neuroprotection. Evidence from animal studies suggests that drug therapy may act on specific transcription factors and target genes that regulate processes such as neuroprotection and neuronal survival. Clinical studies consistently identify changes in prefrontal cortex, hippocampus and amygdala that may be related to the course of illness and may be prevented with successful treatment. Together, these findings suggest that clinically relevant neurobiological correlations may ultimately be identified in patients who respond and remit to treatment. With these and future advances in the neuroscience of psychiatry, it may be possible to identify biological markers that will help in decisions about specific treatments for an individual patient.

À mesure que l'on comprend mieux la neurobiologie des troubles de l'humeur et les modes d'action des antidépresseurs, on met moins l'accent sur les changements de la libération et du métabolisme des neurotransmetteurs pour s'attacher davantage à la régulation de l'expression génique et de la neuroprotection. Des données probantes tirées d'études réalisées sur des animaux indiquent que la pharmacothérapie peut avoir un effet sur des facteurs de transcription spécifiques et des gènes cibles qui régularisent des mécanismes comme la neuroprotection et la survie des neurones. Les études cliniques constatent toujours des changements du cortex préfontal, de l'hippocampe et des corps amygdaliens qui peuvent être reliés à l'évolution de la maladie et qu'il est possible de prévenir au moyen d'un traitement réussi. Ces constatations indiquent globalement qu'il pourrait être possible d'établir éventuellement des corrélations neurobiologiques pertinentes sur le plan clinique chez les patients qui réagissent au traitement et passent en rémission. Ces progrès en neuroscience de la psychiatrie et d'autres à venir pourront permettre d'identifier des marqueurs biologiques qui aideront à prendre des décisions au sujet de traitements adaptés aux patients.

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Introduction

As the neurobiology of mood disorders and the mechanisms of action of antidepressants and mood stabilizing drugs continue to be elucidated, there has been a shift in emphasis from neurotransmission to neuroprotection. Although earlier studies focused on changes in neurotransmitter reuptake and metabolism, recent studies have shifted to regulation of gene expression and neuroprotection. Indeed, these latter interests are consistent with the current clinical focus on the ability of these drugs to lead from illness to remission and to provide prophylaxis against future episodes.

We will review data from animal studies of the mechanisms of action of antidepressants and mood stabilizing drugs and data from clinical studies of patients with major depressive disorder (MDD) and bipolar disorder (BD), with a focus on possible effects on treatment outcome. These data are compelling and may eventually lead to changes in clinical practice in the treatment of mood disorders.

Mechanisms of action of antidepressants and mood stabilizing drugs

There have been many approaches to studying the mechanisms of action of antidepressant and mood stabilizing drugs. The historically important focus on regulation of monoaminergic neurotransmitters has given way to studies on the intracellular pathways linked to those neurotransmitters. From the consistent findings on the action of antidepressant and mood stabilizing drugs on these intracellular pathways, the focus has more recently shifted toward the agents' potential neuroprotective effects, which are downstream to these pathways. These neuroprotective effects may be particularly relevant to understanding the prophylactic effects of both classes of agents.

cAMP-regulated pathways

Most of the clinically relevant antidepressants target either the serotonergic or the noradrenergic pathway (or both). Because the effects of these drugs do not occur for at least several weeks, there has been a focus on specific targets such as signalling pathways coupled to transcription factors and their target genes. Among the most studied are components within the cAMP-regulated pathways such as the GTP-binding proteins (G-proteins), which couple receptors to the effector enzyme adenylyl cyclase, cAMP-dependent protein kinase, and cAMP regulatory element binding protein (CREB) and its phosphorylation (Table 1).[1] Agents from the major antidepressant classes (i.e., tricyclics, serotonin reuptake inhibitors and monoamine oxidase inhibitors) have all been shown to regulate multiple steps

Table 1: Effects of antidepressant and mood stabilizer therapy on neurological targets

Target	Function	Long-term antidepressant treatment or electroconvulsive shock	Mood stabilizers
GTP-binding proteins (G-proteins)	Couple receptors to effector enzyme adenylyl cyclase		May levels
Adenylyl cyclase		↑ basal and stimulated activity	May activity
CAMP-dependent protein kinase		Increases phosphorylation	
cAMP regulatory element binding protein (CREB)		↑ levels ↑ levels of CREB mRNA ↑ CREB immunoreactivity ↑ CRE binding activity	May decrease levels
Brain-derived neutrophic factor (BDNF)	Promotes neuronal survival and neuroprotective	Infusion of BDNF can alleviate despair ↑ BDNF ↑ receptor trkB Blocks of BDNF in response to stress	
Pro-apoptotic genes (p53, Bax), anti-apoptotic gene (Bcl-2), pro-apoptotic enzyme (caspase-3)	Regulate cell death		Lithium: apoptotic genes Lithium/valproic acid:↑ anti-apoptotic genes
Endoplasmic reticulum stress proteins	Neuroprotective		Valproic acid:↑
Hippocampal neurogenesis		↑	↑

Blunted activity, decreased levels or downregulation. ↑ Increased activity, increased levels or upregulation.

in this pathway.[2] Long-term antidepressant treatment increases basal and stimulated adenylyl cyclase activity, increases cAMP-dependent phosphorylation and increases CREB levels.[3] In contrast, mood stabilizers such as lithium have been shown to decrease or blunt the activity of multiple components of this pathway in rat brain.[4] These opposing effects on this pathway may be relevant to their clinical effects.

Transcription factors

In rat hippocampus, long-term antidepressant administration increases levels of CREB mRNA in the CA1, CA3 and dentate gyrus regions of the hippocampus, and leads to increased CREB immunoreactivity and CRE binding activity.[2] This result, found across several different classes of antidepressants, suggests that the upregulation of CREB may be a common target of serotonin and norepinephrine systems, both of which are implicated in the pathophysiology of depression. Long-term administration of electroconvulsive shock (ECS) therapy was also found to increase levels of CREB mRNA, further supporting the potential relevance of changes in CREB levels in the treatment of MDD.[5]

Target genes

CREB, a transcription factor, is a critical step linking short-term changes in signalling molecules with long-term changes in gene expression. There are many potentially relevant target genes regulated by the cAMP signalling pathway that are mediated by CREB and its phosphorylation. One potential target gene, brain-derived neurotrophic factor (BDNF), has recently received a lot of attention as a target of antidepressant drugs. This is largely because of its actions in promoting neuronal survival and neuroprotection and because of evidence that it is modulated by antidepressant drug treatment. In animal studies, repeated stress has been shown to decrease levels of BDNF mRNA in the hippocampus.[6] Conversely, studies have shown that the display of "behavioural despair" in the forced swim test can be alleviated by midbrain infusion of BDNF.[1,6] Thus, there appears to be a correlation between a stress-induced reduction of BDNF levels and depressive-like behaviour. In addition, long-term antidepressant treatment upregulates BDNF and its receptor, trkB, and blocks the downregulation of BDNF in response to stress, indicating that the link between reduced BDNF levels and stress-induced depressive behaviour is robust and pervasive.[4] Repeated administration of ECS increases BDNF mRNA in the rat hippocampus, and this increase persists for up to 48 hours after the administration of the last shock.[7]

Neurogenesis

One of the possible outcomes of increased BDNF expression in the hippocampus is neurogenesis. Long-term antidepressant treatment and ECS can increase the proliferation and survival of new neurons.[8,9] There is some evidence that this may be due to increased differentiation of progenitor cells into neurons, rather than to cell proliferation.[10] Antidepressant treatment may also increase cell survival in regions of the brain that receive input from the granule cells such as the CA3 region.[1] Evidence that neurogenesis occurs in cerebral cortex suggests neurogenesis in this brain region might also be targeted by antidepressant treatment.[11]

A series of studies also supports neuroprotective targets for mood stabilizing drugs. Nonaka and colleagues[12] were the first to show that long-term lithium treatment could protect rat cerebellar cells from *N*-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity. It was later shown that lithium was capable of suppressing expression of the pro-apoptotic genes p53 and Bax, while increasing the expression of the anti-apoptotic gene Bcl-2.[13] More recently, Bijur et al[14] showed that lithium could inhibit the activity of glycogen synthase kinase (GSK-3β) and attenuate the activation of the pro-apoptotic enzyme caspase-3, thus protecting the cell from death. These results suggest that lithium may exert its neuroprotective effect at more than one site or signalling pathway within the cell. Valproic acid has been shown to upregulate the expression of the neuroprotective endoplasmic reticulum stress proteins and the anti-apoptotic protein Bcl-2 and, thus, may also have neuroprotective effects that are mediated through unique pathways within the cell.[15,16] One recent study suggests that lithium may also increase neurogenesis in some of the same hippocampal regions affected by antidepressant treatment (i.e., dentate gyrus).[17]

Clinical studies in patients with mood disorders

Among the variety of approaches that have been used to study targets of drugs in patients with mood disor-

ders, compelling data come from tissue, brain imaging and postmortem brain studies. Studies in peripheral cells from patients before and after drug treatment allow for multiple samples to be obtained from the same individual. Brain imaging studies, including positron-emission tomography and magnetic resonance imaging, also allow for multiple determinations. However, although postmortem brain studies have provided valuable information, they inherently do not allow for multiple samples or control over drug treatment or mood state.

Peripheral blood cell studies

There is evidence in peripheral cells such as leukocytes and platelets that a number of components of the cAMP pathway may be regulated in response to specific drug treatment. The activity of adenylyl cyclase in blood cells is blunted in depressed subjects and has been shown to increase after treatment with antidepressants and ECS.[18,19] In studies of platelets and leukocytes from subjects with BD, there is some evidence that G-protein abnormalities in the cAMP system are dependent on mood state and can be normalized after successful treatment.[20,21] Other studies on peripheral cells have found abnormalities in this pathway in euthymic, manic and depressed subjects with bipolar disorder on and off treatment, including those receiving multiple medications.[22] In one large study, the further downstream the target in the cAMP signalling cascade, the less likely it was to change back to normal after treatment.[23]

Postmortem brain studies

In postmortem studies, treatment effects can be measured directly in brain. Although multiple sampling cannot be done, treatment effects can also be estimated by careful review of medical records and interviews with surviving relatives, which is now standard practice in many brain banks around the world.

Several groups, using independent tissue samples, have found blunted adenylyl cyclase activity in depressed subjects, although the results for levels of G-protein subunits, which couple receptors to the enzyme, are less consistent.[4,24] Cerebral cortical CREB levels are also increased in subjects taking antidepressants at the time of death,[24] a finding similar to that seen in rat brain. Moreover, hippocampal BDNF immunoreactivity, and levels of its receptor, trkB, are also increased in subjects taking antidepressants.[25]

In contrast to the numerous peripheral blood cell studies showing treatment effects in subjects with BD, less is known about the effects of treatment or response on the basis of postmortem findings. At least some data suggest that treatment with lithium or the mood stabilizing anticonvulsants may decrease G-protein levels, adenylyl cyclase activity and CREB levels in cerebral cortex of subjects with BD.[4,24]

Since antidepressants and mood stabilizing drugs target neuroprotective pathways, it is not surprising that investigators have counted cells in tissue from patients with mood disorders. As reviewed by Rajkowska,[26] postmortem studies in those with MDD and BD provide evidence of a number of changes, including cell loss and atrophy, in prefrontal cortex. Cell number may also be increased in hypothalamus,[27] which may be relevant to the prominent neurovegetative symptoms of these disorders. Recent studies on postmortem hippocampal tissue have used a technique called Timm staining to measure neuronal sprouting, which may compensate for cell loss in this brain region.[28] In subjects with BD, we found evidence of increased Timm staining in dentate gyrus, which may be evidence of sprouting of mossy fibre collaterals from the granule cells in this region. In this same sample, there was an association between antidepressant treatment and increased Timm staining in individuals with MDD and BD. It remains to be clarified which of these changes are related to the pathophysiology of these disorders and which are targeted by specific treatments. It also remains to be determined whether there are changes in hippocampal cell number in subjects with mood disorders and whether new growth is functional. The results of these studies will be of great interest once completed.

Brain imaging studies

Brain imaging studies have provided a vast amount of information about the neuroanatomic correlates of both MDD and BD. Change in either size or function of the prefrontal cortex, hippocampus and amygdala are consistently reported in studies of subjects with these disorders.[29,30] Among the most interesting of these is the finding that hippocampal volume may be reduced in subjects with MDD and that this may be related to the length of illness.[31,32] Whether these changes can be

prevented by successful treatment is not yet known. In a series of studies, Mayberg et al[33] reported that chronic treatment and clinical response to fluoxetine was associated with a reciprocal pattern of decreased metabolism in limbic structures and increased metabolism in selected cortical regions. They also reported a reversal of metabolic patterns apparent at baseline in MDD subjects who respond to fluoxetine treatment.

Conclusions

An increasing body of evidence from animal studies suggests that antidepressants and mood stabilizing drugs may act on specific transcription factors and target genes that regulate processes such as neuroprotection and neuronal survival. These lasting changes are likely important in understanding treatment response and outcomes of patients with mood disorders. Clinical studies consistently identify changes in prefrontal cortex, hippocampus and amygdala that may be related to the course of illness and may be prevented with successful treatment. Together, these findings suggest that clinically relevant neurobiological correlations may ultimately be defined in patients who respond and remit to treatment.

The advances in neuroscience as applied to psychiatry are promising and may eventually help predict response to specific agents. It is conceivable that, in the future, biological markers may guide decisions about specific treatments for particular patients. Ironically, it may be the understanding of the neurobiology of full remission and prevention of relapse, rather than the short-term effects of antidepressant and mood stabilizing drugs, that is particularly relevant in the treatment of our patients.

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