Dissecting the Pathophysiology of Depression with a Swiss Army Knife

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In this issue of Neuron, Hen and colleagues shed new light on the behavioral effects of fluoxetine, one of the most commonly prescribed antidepressants. This report prompts us to revisit our understanding of the neural circuitry mediating mood disorders and also provides a framework for developing new antidepressant treatments.

“...I’m like some king in whose corrupted veins
Flows aged blood; who rules a land of rains;
Who, young in years, is old in all distress;
Who flees good counsel to find weariness...”
— Charles Baudelaire (1821–1867), Spleen

Two conflicting views of mental illness prevailed in the first half of the nineteenth century. The so-called “Moral theorists” looked upon mental illness as an affliction of the mind that could be treated with kindness and through appeal to the intellect. Proponents of this school of thought emphasized spiritual causes in their treatment of madness. Other physicians thought that a defective brain was the culprit of mental illness. Dubbed the “physicalists,” these doctors attempted to treat their patients by applying the most current knowledge of brain research. Inspired by the physicalist tradition, David et al. (2009) conduct a study that sheds new light on the nature of the disrupted circuits in a model of depression, as well as the numerous mechanisms by which antidepressants can correct these deficits.

Affective disorders, including ailments such as depression and anxiety, are among the most prevalent of all mental health diagnoses. Depression or anxiety can severely disrupt life by affecting appetite, sleep, work, and social relationships. Selective Serotonin Reuptake Inhibitors (SSRIs), like fluoxetine, are the most commonly prescribed drugs for such mood disorders. However, very little is known regarding the molecular mechanisms and the specific neural circuits that underlie these drugs’ effects.

As antidepressants have established themselves as the predominant treatment for major depressive disorders, the development of new treatments is never-ending. In the process, animal models of anxiety/depression are commonly used to screen novel compounds for antidepressant properties, although the clinical relevance and efficiency of such models is debatable. For example, the behavior produced by unpredictable chronic mild stress in animals (Heine et al., 2004), though widely used, is difficult to consistently replicate. Alternatively, mice may be supplied with exogenous corticosterone (Gourley et al., 2008), a hormone produced in the adrenal gland in response to stress. Chronically elevated glucocorticoid levels are found in several commonly used animal models of depression, including restraint stress or forced swimming. There is also evidence from human studies that depression is often associated with dysfunctions of the hypothalamic-pituitary-adrenal axis (Holsboer, 2008).

In a study detailed in this issue of Neuron, David et al. (2009) utilize chronic corticosterone treatment to develop a mouse model exhibiting hallmark characteristics of anxiety and depression. They find that chronic fluoxetine treatment reverses the behavioral deficits induced by chronic corticosterone. Additionally, they investigate a possible link between affective state disorders in this model and hippocampal neurogenesis. While the effect of fluoxetine on Novelty Suppressed Feeding is neurogenesis independent (i.e., blocked by X-irradiation), SSRI effects on Open Field and Forced Swim Test are neurogenesis independent (Figure 1). Importantly, antidepressants are effective only in the corticosterone-treated animals.

A key question is whether studying the effects of fluoxetine on corticosterone-treated mice is relevant to the antidepressant’s action in humans. Previously, Tsankova et al. (2006) demonstrated that both imipramine (a tricyclic antidepressant) and fluoxetine can reverse social avoidance in humans affected with defeat stress, but not in control subjects. The “corticosterone model” used by David et al. seems to mimic these observations.

According to a recent theory, the failure of adult hippocampal neurogenesis sets the stage for the biological and cellular basis of major depression (Sahay and Hen, 2007). Approximately 9000 neurons are produced daily in the dentate gyrus (Cameron and McKay, 2001), and reduced levels of neurogenesis could lead to less adaptive behavior, which may manifest itself through depressive states marked with a helpless predisposition. People diagnosed with major depression presumably suffer from a deficit of neurogenesis: they exhibit recollection-memory deficits that are characteristic of hippocampal damage, accompanied by a reduction in hippocampal volume that correlates with total illness duration (MacQueen et al., 2003). However, the still unresolved function of the adult-generated neurons (Lledo et al., 2006) is the missing piece in this hypothesis.

It has been known for many years that antidepressants increase hippocampal neurogenesis (Malberg et al., 2000) and that some of the behavioral effects of antidepressant treatment require adult
neurogenesis (Santarelli et al., 2003). However, in rodents deprived of adult neurogenesis, some of the behavioral effects of chronic antidepressant treatment are still observed. Also, transcranial magnetic stimulation, another effective treatment for depression, does not stimulate adult neurogenesis. It has been suggested that drugs with antidepressant activity mediate their effects through either neurogenesis-dependent or neurogenesis-independent mechanisms (Surget et al., 2008). Here, David et al. provide a significant conceptual advance by demonstrating that the effects of a single drug, fluoxetine, are mediated through both neurogenesis-dependent and neurogenesis-independent pathways, therefore reconciling the initial discrepancies (Figure 1).

Stimulation of adult neurogenesis in the dentate gyrus is only one of several mechanisms through which antidepressants exert their behavioral actions. Here, the authors demonstrate that a chronic corticosterone regimen followed by fluoxetine treatment affects gene expression not only in the hippocampus, but also in the hypothalamus and amygdala. Thus, the neurogenesis-independent pathway might be linked to signaling changes in these other brain areas. The authors show that only three genes, all related to G protein-coupled receptors (β-arrestin 1, β-arrestin 2, and Gria2 proteins), have decreased expression in the hypothalamus of depressed animals. These reduced levels are reversed by fluoxetine treatment. Furthermore, genetic ablation of β-arrestin 2 blocked several of the behavioral effects of fluoxetine, suggesting that β-arrestins play an essential role in the anxiolytic/antidepressant activity of fluoxetine (Figure 1). Previous results from Caron and others had hinted that β-arrestin 2 KO mice might exhibit an anxiety phenotype (Beaulieu et al., 2008), and β-arrestins have been suggested to mediate the effects of lithium, a drug commonly used to treat bipolar disorder. The observation that β-arrestin-2-deficient mice are unresponsive to fluoxetine in most behavioral tests (Figure 1) raises the distinct possibility that there are common mechanisms underlying both bipolar disorder’s and unipolar major depression’s response to treatment, which may reflect the fact that these disorders share common genetic determinants such as a modulator of glucocorticoid receptor sensitivity, FKBP5 (Willour et al., 2009). Altogether, the report by David et al. contributes to erecting a more unified theory of depression.

Are the therapeutic effects of fluoxetine also dependent on multiple distinct mechanisms? Might antidepressants work through a combination of effects on both cognitive functions and affect? Would this result in a distinction between the antidepressant-induced effects on the hippocampus and those in other limbic structures? It has been suggested that the effects of antidepressants on mood may be neurogenesis independent while those on anxiety may be neurogenesis dependent (Bessa et al., 2009). This is an important question and suggests that drug developers need to determine whether compounds that directly stimulate neurogenesis would be effective as antidepressants or whether they would only ameliorate cognitive deficits.

Although unraveling the pathophysiology of depression is a unique challenge, it is by no means a new one. Hippocrates described the clinical presentation of depression in the fourth century B.C., attributing the ailment to excessive amounts black bile, or “melan chole” (from which the word “melancholy” was coined). Ever since the ancient Greek physicians, we have made substantial progress in bringing to light the complex brain mechanisms involved in affective disorders, particularly in deciphering the molecular biology of depression (Krishnan and Nestler, 2008). Despite these efforts, enormous gaps in the knowledge of mood disorders and their treatments remain.

While the report from David et al. provides valuable insights with major breakthroughs, it raises more questions than it answers. What exactly can research on rodent behavior tell us about human psychopathology? Human psychiatric disorders are complicated amalgams of cognitive, affective, and behavioral abnormalities. We may be able to model features of one of these dimensions in rodents (such as helplessness or anhedonia), but we should be fully aware that we are only studying an aspect of the disorder, not the disorder itself per se. Major depressive disorder in humans is certainly more than the sum of its observable parts. Also, how adult hippocampal neurogenesis contributes to the regulation of affect is still an open question. More work is necessary to understand the link between adult hippocampal neurogenesis and the action of some antidepressant drugs. Thus far, we have little more than phenomenological reports. In order to address these questions, novel animal models need to be developed that incorporate the powerful array of molecular and anatomical tools available today, while employing a systems approach to reflect the powerful bidirectional interactions between peripheral organs and the brain. There is no doubt
that Hen and colleagues have provided us with a renewed impetus for this quest.

REFERENCES


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In this issue of Neuron, Johnson et al. employ a unique whole-genome exon-level analysis of the developing human brain showing that 76% of genes are expressed along with unexpectedly high levels of differential expression. These results have important consequences for understanding normal and pathological function and provide implications about the uniqueness of being human.

The human brain is beyond doubt the most sophisticated computational machine known to man, about whose self-construction or function we know tantalizingly little. The developmental study from Sestan and his colleagues makes a major contribution to our knowledge of the former area with far-reaching implications for the second (Johnson et al., 2009 [this issue of Neuron]). They report on the analysis of whole-genome exon-level expression of 13 regions in the midgestation human brain. This technique allows the identification of alternative splicing, which concerns 75% of the human multixenon genes. This is an important advance because alternative splicing is an established mechanism for gene diversification that can generate multiple proteins, and it is known to have important roles in normal and pathological brain function.

Rodents are the most widely used model for the investigation of brain development. However, alongside a number of core mechanisms that are conserved between rodents and primates, there are major differences in the nature and timing of ontogenetic processes characterizing primate corticogenesis (Dehay and Kennedy, 2007). Studies of human brain development, combined with interspecies comparisons, are therefore much needed in order to progress in understanding how the highly developed cortical areas in humans have acquired the capacity to support the rich repertoire of complex cognition and behaviors characteristic of our species. Because the Exon Array platform provides unparalleled resolution in its coverage of the genome (it reveals the prevalence and importance of alternative splicing and other fine transcriptional regulation), the work of Sestan and his colleagues opens the exciting possibility of better nailing down the evolutionary and developmental mechanisms that underlie unique human cognitive abilities such as language, abstract thinking, and creativity.

One key aim in the field of developmental neurobiology is to unravel the genetic mechanisms that underlie the specification of the identity of cortical areas. Because of the sheer resolution power of the Exon Array technology combined with an astute experimental design, this work represents a step forward in the search for the Holy Grail of neurodevelopmental science.