New mouse model of depression/anxiety enhances understanding of antidepressant drugs

May 27 2009

A recent study finds that the antidepressant effects of drugs like Prozac involve both neurogenesis-dependent and -independent mechanisms, a finding that may lead to development of better treatments for depression and anxiety. The research, published by Cell Press in the May 28th issue of the journal *Neuron,* utilizes a new experimental mouse model of depression/anxiety that is the first to permit simultaneous examination of multiple effects of antidepressant treatment in the same animal.

The specific molecular influences of selective serotonin reuptake inhibitors (SSRIs) and other types of antidepressants commonly prescribed for treatment of depression and anxiety disorders are not well understood. "Recently, compelling work in rodents has suggested that SSRIs may stimulate changes in a brain region called the hippocampus as well as other brain structures," says study author Dr. Denis J. David from the University of Paris-Sud. "For example, anxiety/depression-like changes in behavior have been linked with a decrease in cell proliferation in the hippocampus, a change that is reversed by antidepressants."

Dr. David, Dr. Rene Hen from Columbia University, and their colleagues created a mouse model of depressive and anxiety disorders to investigate mechanisms of antidepressant action. Previous research confirmed that long-term exposure to glucocorticoids induces anxiety and a depressive-like state in rodents and elevated glucocorticoid levels

have been linked with depression and anxiety in humans. "We developed an anxiety/depression-like model based on elevation of glucocorticoid levels that offered an easy and reliable alternative to existing models," explains Dr. David.

Chronic antidepressant treatment reversed the behavioral dysfunctions and inhibition of hippocampal neurogenesis observed in the experimental mice. When hippocampal neurogenesis was prevented, the efficacy of Prozac was blocked in some but not all of the behavioral paradigms. The researchers went on to identify candidate genes whose expression was decreased in a brain region called the hypothalamus and normalized by Prozac. Mice deficient in one of these genes, ?-arrestin 2, displayed a reduced response to Prozac in multiple behavioral tasks, indicating that ?-arrestin signaling is necessary for the antidepressant effects of Prozac.

This finding suggests that both neurogenesis-dependent and -independent mechanisms underlie antidepressant actions. "The big unanswered question is whether future drugs that directly stimulate neurogenesis will be as effective as popular antidepressants or will only ameliorate cognitive deficits," says Dr. Hen. "To begin to answer this question we are using our paradigm to test a series of compounds that may stimulate neurogenesis more directly or compounds that directly target the hypothalamus. Ultimately, it is the success of these new compounds in the clinic that will establish the predictive value of the biomarkers we have identified in this report."

Source: Cell Press (news : web)