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Review

Childhood and adolescent depression: Why do children and adults respond differently to antidepressant drugs?

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Abstract

Childhood and adolescent depression is an increasingly problematic diagnosis for young people due to a lack of effective treatments for this age group. The symptoms of adult depression can be treated effectively with multiple classes of antidepressant drugs which have been developed over the years using animal and human studies. But many of the antidepressants used to treat adult depression cannot be used for pediatric depression because of a lack of efficacy and/or side effects. The reason that children and adolescents respond differently to antidepressant treatment than adults is poorly understood. In order to better understand the etiology of pediatric depression and treatments that are effective for this age group, the differences between adults, children and adolescents needed to be elucidated. Much of the understanding of adult depression has come from studies using adult animals, therefore studies using juvenile animals would likely help us to better understand childhood and adolescent depression. Recent studies have shown both neurochemical and behavioral differences between adult and juvenile animals after antidepressant treatment. Juvenile animals have differences compared to adult animals in the maturation of the serotonergic and noradrenergic systems, and in dose of antidepressant drug needed to achieve similar brain levels. Differences after administration of antidepressant drug have also been reported for adrenergic receptor regulation, a physiologic hypothermic response, as well as behavioral differences in two animal models of depression. The differences between adults and juveniles not only in the human response to antidepressants but also with animals studies warrant a specific distinction between the study of pediatric and adult depression and the manner in which new treatments are pursued.
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1. Adult depression

Depression describes a transient mood state experienced by virtually all individuals at some time in their life, generally in response to stressful life events as well as a serious clinical disorder. Major depressive disorder (MDD, American Psychiatric Association's DSM-IV manual) is a debilitating and serious mental illness that affects approximately 2–5% of the population worldwide, with a lifetime prevalence of around 15%. This disorder significantly interferes with the ability of the affected person to function normally. The symptoms include a persistent sad or ''empty'' mood and feelings of hopelessness and worthlessness, changes in sleep and appetite, loss of interest in normally pleasurable activities; difficulty in concentrating, remembering, making decisions, and thoughts of death or suicide (Fava and Kendler, 2000). Patients formerly hospitalized with depression are at high risk (>10%) of committing suicide. When left untreated major depressive disorder can reduce the quality of a patient's life for months if not years at a time. In addition to the emotional and physical pain caused by depression, the economic cost in the United States alone is estimated at $70 billion annually, and The World Health Organization projects by the year 2020, depression will be second only to heart disease as the leading cause of disability worldwide. In this review, we are concerned with the clinical syndrome, major depressive disorder, not the ubiquitously experienced temporary change in mood.

In adults, depression can be successfully treated with psychotherapeutic methods (i.e., cognitive-behavioral therapy) and electroconvulsive treatment, as well as with several classes of antidepressant drugs, as summarized in Table 1. In general, the various antidepressant drugs have similar efficacies,

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Table 1
Antidepressant drug classes

Class	Examples	Mechanism
Monoamine oxidase inhibitors (MAOI)	Phenelzine	Inhibits the metabolism of norepinephrine, serotonin and dopamine
Tricyclic antidepressants (TCA)	Desipramnine imipramine	Blocks the norepinephrine and serotonin transporters
Selective serotonin reuptake inhibitors (SSRI)	Fluoxetine citalopram	Blocks the serotonin transporter
Atypical antidepressants	Bupropion mirtazapine	Alters norepinephrine, serotonin and/or dopamine neurotransmission
Selective norepinephrine reuptake inhibitors (NRI)	Reboxetine	Blocks the norepinephrine transporter
Serotonin norepinephrine reuptake inhibitors (SNRI)	Venlafaxine	Blocks the norepinephrine and serotonin transporters

although there is significant variability in individual responsiveness (Delgado, 2004). The currently available evidence suggests that the initial step in the mechanism of action of these antidepressants is an increase in monoamine levels. In spite of the fact that levels increase to 100–300% within hours of the initiation of drug treatment, significant therapeutic improvement usually does not occur for 2–4 weeks (Delgado, 2004). Thus, it appears that other adaptive changes, such as those in G protein-coupled receptors, are necessarily involved in the mechanism of action of antidepressant drugs (Catapano and Manji, 2007).

1.1. Animal studies of adult depression

Many animal studies have been conducted over the years related to depression and the action of antidepressant drugs. Two of the major types of these studies are those involving behavior and those involving neurochemical alterations in the brain. These studies have been essential for our current understanding of depression and antidepressant drug action, as well as for the development of new antidepressant treatments.

1.1.1. Behavioral animal models of adult depression and antidepressant drug action

Because human depression is at least in part an abnormal response to stress (Leonard, 2001), many of the animal models that relate to depression and antidepressant drug action are based on the animal's response to stress (Nestler et al., 2002; Vollmayr and Henn, 2003). Of the available animal models of human depression, including the chronic mild stress model, the olfactory bulbectomized rat, and the Flinders Sensitive Line, the learned helplessness and the forced-swim test are the best replicated and accepted (Kelly and Leonard, 1998).

The forced-swim test, also known as behavioral despair, refers to a paradigm in which rodents are forced to swim in a confined space on two occasions and is widely used to predict antidepressant efficacy (Lucki, 1997; Porsolt et al., 1977). This test consists of placing a rat or a mouse in a cylinder of water from which there is no escape and measuring the animal's behavior for 5 min. Initially, rodents display escape-oriented behaviors including swimming and vigorous attempts to climb the wall of the cylinder. Eventually this behavior changes to 'immobility', which is defined as movements that are just sufficient to keep its head above water. Antidepressants of all major classes, as well as repeated electroconvulsive shock, reduce immobility and increase swimming or climbing behaviors in the forced-swim test. Remarkably, selective serotonin re-uptake inhibitors (SSRIs), which increase extracellular serotonin levels, increase swimming behavior, whereas drugs acting primarily to increase extracellular levels of norepinephrine or dopamine increase climbing behavior (Cryan et al., 2002, 2005).

Learned helplessness refers to a stress-induced behavioral depression (Seligman and Maier, 1967). Learned helplessness behavior in the rat is normalized by all classes of antidepressant drugs and by electroconvulsive shock after repeated (but not acute) administration, but not by antipsychotic, antianxiety, sedative, or stimulant drugs (Sherman et al., 1982). The learned helplessness model, as originally developed for rodents, is performed in two sessions. In the first session, inescapable shock stress is delivered via an electrified grid floor or via tail electrodes. Levels of shock used are low (1 mA), and when experienced by humans, characterized as unpleasant, rather than painful. The shock is presented in a random pattern, making it unpredictable, during the course of 40–120 min. In the second session, the animal is given an opportunity to escape the shock, by pressing a lever or moving across a shuttle box. Naive, non-stressed rats will characteristically learn to escape the aversive shock stimulus efficiently, reliably, and quickly. Rats that have experienced previous inescapable, unpredictable shock demonstrate a range of behavior in the escape test, with some animals performing in a manner similar to naive, non-stressed rats, and some showing varying deficits. Failure to escape, or relatively poor escape performance, is defined as learned helplessness. Although the proportion of rats which demonstrate learned helplessness after inescapable stress varies, depending on factors such as strain, duration of inescapable stress, and the escape test used, this model replicates an important feature of human depression in that similar stress results in some individuals developing depression whereas others do not.

A second important advantage of this model is that the neurochemistry of those animals which exhibit learned helplessness can be compared to those animals which do not. In healthy, non-depressed persons, antidepressant drugs do not have significant effects upon mood. In depressed persons, antidepressant drugs have marked and profound effects upon mood. Thus, in understanding which neurochemical actions of the antidepressant drugs are functionally related to their antidepressant effects, by studying the drug effects in animals that have developed learned helplessness is likely to yield additional insight over studies of healthy, non-depressed animals.

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