from depression to resume a much higher quality of life, today’s researchers are making the discoveries that will lead to the antidepressants of the future.

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Selecting selectivities and the neuropharmacology of antidepressant drug action

A commentary

David B. Bylund

Depression, specifically Major Depressive Disorder, affects approximately 17% of the population and is a major cause of disability worldwide. A recent World Health Organization report predicts that depression will be the leading cause of disability and premature death in the industrial world by the year 2020 (1). The history of the development of antidepressant drugs is one of serendipity, brilliant insights, and lots of hard work.

First generation antidepressant drugs were found to inhibit the reuptake or metabolism of norepinephrine, serotonin, and dopamine. Unfortunately, they also had prominent autonomic and other side effects due to having relatively high affinity for some neurotransmitter receptors, particularly alpha adrenergic, muscarinic, and histamine receptors (2). The development of the selective serotonin reuptake inhibitors (SSRIs) was a major advance because they significantly reduced these side effects. In addition, this class of drugs selectively inhibits the serotonin transporter (SERT) as compared to the norepinephrine (NET) and dopamine (DAT) transporters. However, as is clearly indicated by the selective norepinephrine reuptake inhibitors such as reboxitine (Edronax), which are equally efficacious with the SSRIs in treating depression, the important advantage of the SSRIs is not their selectivity for SERT over NET, but their lower affinity for the biogenic amine receptors mediating the adverse effects.

Some of the more recently developed antidepressant drugs are selective for several monoamine transporters. It has been suggested that balanced or dual reuptake inhibitors such as venlafaxine (Effexor) (i.e., drugs that inhibit both SERT and NET) may be superior to single reuptake inhibitors in the treatment of depression, although the clinical evidence for such claims is currently rather weak (3). More recently, triple reuptake inhibitors, which inhibit SERT, NET, and DAT are being developed as new antidepressant treatments. These compounds have been hypothesized to have a more rapid onset of activity and better efficacy over single or dual reuptake inhibitor antidepressants in part due to the addition of the dopamine component (4). Similarly, there is renewed interest in the potential use of monoamine oxidase inhibitors to elevate levels of serotonin, norepinephrine, and dopamine in the treatment of depressive disorders.

All of this at least suggests that the most selective drug may not necessarily be the best. As new antidepressant drugs are being developed, selecting the appropriate selectivities is an important component of the overall strategy. In order to understand how to select, and where to be selective, basic studies in organ systems and intact animals are critical (5).

For example, the selectivity for SERT over NET may be a critical factor in the treatment of pediatric depression. In contrast to adult depression for which there are over 33 drugs approved by the US Food and Drug Administration, there is currently only one drug approved for adolescent depression, namely fluoxetine (Prozac). The recent Treatment of Adolescents with Depression Study found fluoxetine combined with cog-

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nitive behavioral therapy to be the most efficacious treatment (6). Fluoxetine alone was also efficacious; however, cognitive behavioral therapy alone was no better than placebo in the treatment of depression. In spite of the recent publicity on suicidal ideation of adolescents taking fluoxetine, the current evidence indicates that, in general, the benefits outweigh the risks (7).

Controlled clinical trials have not shown the tricyclic antidepressants, such as desipramine (Norpramin) which act largely through the noradrenergic system, to be any better than placebo in treating pediatric depression. The biological basis for this is not understood, but it has been suggested that a contributing factor is the relatively slow maturation of the noradrenergic system in the brain as compared to the serotonin system (8). The recently developed animal models of pediatric depression should facilitate a better understanding of the differences in response to antidepressant drugs of children and adolescents as compared to adults, and perhaps will help provide insights into new treatment modalities for pediatric depression (9).

As we move into the era of personalized medicine, which is based on the concept of selectivity in treatment of individual patients, it will be important to remember that the complexity of intact organisms with all their interconnected pathways and feedback mechanisms, will continue to require innovative basic and clinical studies to select those selectivities which are most beneficial.

REFERENCES

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