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Mechanism of calming hyperactivity by psychostimulant drugs identified

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It has long been known that psychostimulant drugs have the paradoxical effect of reducing hyperactivity. [Psychostimulant drugs include methylphenidate – known by the trade names Ritalin, Concerta, and Methylin – and methamphetamine]. Since the mid-1950s, millions of children and adults have been prescribed stimulant medications to control attention deficit hyperactivity disorder (ADHD). But for more than seven decades, since the first experiment that gave an amphetamine drug to children diagnosed with behavioral problems, scientists have not known how stimulants work to control hyperactivity.

Now, a researcher at SUNY Downstate Medical Center, working with colleagues in Mexico, has identified the probable mechanism by which certain stimulants accomplish this paradoxical reduction of motor activity. David Erlij, MD, PhD, professor of physiology and pharmacology at SUNY Downstate, and fellow researchers have identified a network of nerve terminals where stimulation of dopamine D4 receptors depresses motor activity. "This network is localized deep in the brain, in the basal ganglia and the thalamus," says Dr. Erlij, "and its responses explain the reduction in motor activity caused by psychostimulants."

The findings were published in a recent edition of the journal, *Neuropharmacology*, and were conducted in an animal model. Dr. Erlij notes, "When, in 1937, Dr. Charles Bradley administered Benzedrine to a group of children with hyperactivity and learning disorders and discovered that 'fourteen children responded in a spectacular fashion,' a

new era of psychopharmacology was inaugurated. Bradley showed, for the first time, that taking a pill could successfully treat a behavioral abnormality. Eventually, this discovery led to the widespread use of psychostimulant drugs in the treatment of ADHD."

"Despite their well established beneficial effects, it was not understood why psychostimulant drugs, which normally amplify the stimulatory responses of dopamine signals, reduce hyperactivity," says Dr. Erlij. "Our results suggest that enhancing dopamine D4 transmission in the basal ganglia and the thalamus is likely part of the mechanism of the therapeutic effects of psychostimulants on ADHD."

Dr. Erlij adds that the therapeutic action of psychostimulants in ADHD suggests that this condition is caused by abnormalities of dopamine signaling in the brain, and that, in ADHD patients, the dopamine D4 receptor gene is abnormal. He concludes, "Now that we know with some precision where calming of hyperactivity is likely taking place in the brain, it may be possible to develop new and better treatment modalities."

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