Scientists explain how ketamine vanquishes depression within hours

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(Medical Xpress)—Many chronically depressed and treatment-resistant patients experience immediate relief from symptoms after taking small amounts of the drug ketamine. For a decade, scientists have been trying to explain the observation first made at Yale University.

Today, current evidence suggests that the pediatric anesthetic helps regenerate synaptic connections between brain cells damaged by stress and depression, according to a review of scientific research written by Yale School of Medicine researchers and published in the Oct. 5 issue of the journal *Science*.

Ketamine works on an entirely different type of neurotransmitter system than current antidepressants, which can take months to improve

symptoms of depression and do not work at all for one out of every three patients. Understanding how ketamine works in the brain could lead to the development of an entirely new class of antidepressants, offering relief for tens of millions of people suffering from chronic depression.

"The rapid therapeutic response of ketamine in treatment-resistant patients is the biggest breakthrough in depression research in a half century," said Ronald Duman, Elizabeth Mears and House Jameson Professor of Psychiatry and Professor of Neurobiology.

Duman and George K. Aghajanian, also professor of psychiatry at Yale, are co-authors of the review.

Understanding how ketamine works is crucial because of the drug's limitations. The improvement in symptoms, which are evident just hours after ketamine is administered, lasts only a week to 10 days. In large doses, ketamine can cause short-term symptoms of psychosis and is abused as the party drug "Special K."

In their research, Duman and others show that in a series of steps ketamine triggers release of neurotransmitter glutamate, which in turn stimulates growth of synapses. Research at Yale has shown that damage of these synaptic connections caused by chronic stress is rapidly reversed by a single dose of ketamine.

The original link between ketamine and relief of depression was made at the Connecticut Mental Health Center in New Haven by John Krystal, chair of the department of psychiatry at Yale, and Dennis Charney, now dean of Mt. Sinai School of Medicine, who helped launch clinical trials of ketamine while at the National Institute of Mental Health.

Efforts to develop drugs that replicate the effects of ketamine have produced some promising results, but they do not act as quickly as

ketamine. Researchers are investigating alternatives they hope can duplicate the efficacy and rapid response of ketamine.

More information:

Ketamine Timeline: A new model of rapid-acting antidepressant

1980's

Evidence emerges that the neurotransmitter glutamate and N-methyl-D-aspartate (NMDA) glutamate receptors play a key role in higher cortical functions.

1990's

Yale investigators at the VA Connecticut Healthcare System and Abraham Ribicoff Research Facilities of the Connecticut Mental Health Center utilize ketamine as a probe to explore the underlying mechanisms of common psychiatric disorders including schizophrenia and alcoholism. A test of ketamine's effects on patients with major depression is initiated. Almost immediately, the scientists begin hearing evidence of the rapid-acting antidepressant effects of ketamine. These effects appeared within hours and lasted for several days.1, 2

2000

The results of the first placebo-controlled, double-blinded trial to assess the treatment effects of ketamine in patients with depression are published in Biological Psychiatry. The findings, by Yale researchers working at the VA Connecticut Healthcare System and the Connecticut Mental Health Center, outline the rapid antidepressant effects of the

compound. The compelling results suggest a potential role for NMDA receptor modulating drugs in the treatment of depression.3

2006

The 2000 Yale findings are replicated by a team at the National Institute of Mental Health.4 The NIMH team includes a Yale Department of Psychiatry alumnus and co-author of the original Biological Psychiatry article.

2010

Yale research suggests an explanation for the rapid antidepressant effects of ketamine. Results published in Science demonstrate that a single dose of ketamine leads to an increased number and function of new synapses in the rodent prefrontal cortex. This restoration of connections between brain cells, a process called "synaptogenesis," is a much quicker process than forming entirely new neurons while accomplishing the same result of enhanced brain connectivity and circuit activity.5

2011

Yale-led study published in Biological Psychiatry demonstrates that the atrophy of dendrites caused by chronic stress in rodents may be reversed by administration of ketamine.6

References

1 Krystal, J.H., Karper, L.P., Seibyl, J.P., Freeman, G.K., Delaney, R. Bremner, J.D., Heninger, G.R., Bowers, M.B. Jr, Charney, D.S. 1994 Subanesthetic effects of the noncompetitive NMDA antagonist,

ketamine, in humans. Arch Gen Psychiatry 51, 199-214. www.ncbi.nlm.nih.gov/pubmed/8122957

2 Krystal, J.H., Petrakis, I.L., Webb, E., Cooney, N.L., Karper, L.P., Namanworth, S., Stetson, P., Trevisan, L.A, Charney, D.S. 1998 Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiatry 55, 354-360 www.ncbi.nlm.nih.gov/pubmed/9554431

3 Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., Krystal, J.H. 2000 Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47, 351–354. www.ncbi.nlm.nih.gov/pubmed/10686270

4 Zarate, C.A. Jr., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K. 2006 A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63, 856–864. www.ncbi.nlm.nih.gov/pubmed/16894061

5 Li, N., Lee, B., Liu, R.J., Banasr, M., Dwyer, J.M., Iwata, M., Li, X.Y., Aghajanian, G., Duman, R.S. 2010 mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329, 959–64. www.ncbi.nlm.nih.gov/pubmed/20724638

6 Li, N., Liu, R.J., Dwyer, J.M., Banasr, M., Lee, B., Son, H., Li, X.Y., Aghajanian, G., Duman, R.S. 2011 Glutamate N-methyl-D-aspartate receptor antagonists rapidly reverse behavioral and synaptic deficits caused by chronic stress exposure. Biol Psychiatry 69, 754–761. www.ncbi.nlm.nih.gov/pubmed/21292242

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