mTOR: A key brain signaling mechanism for rapidly acting antidepressants

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Two years ago, mammalian target of rapamycin or mTOR, a signaling protein, was identified as a key mediator of the antidepressant effects of ketamine, the first rapidly acting antidepressant medication to be identified.

Several years later, a group at the National Institutes of Mental Health Intramural Program reported that scopolamine, a muscarinic acetylcholine receptor antagonist, also produced rapidly appearing antidepressant effects, similar to the actions of ketamine.

Together these findings represent one of the most significant advances in the field of depression in recent years.

Now, new results reported in the current issue of *Biological Psychiatry* by researchers at the Yale University School of Medicine demonstrate that scopolamine causes rapid activation of mTOR signaling and increased number of synaptic connections in the prefrontal cortex.

The prefrontal cortex is an important brain region, involved in executive and cognitive functioning, decision-making, planning, and the expression of personality. It is also implicated in the pathophysiology and treatment of depression.

"These effects are similar to the actions of ketamine, showing that two drugs with completely different receptor blocking profiles have common downstream actions linked to rapid antidepressant responses," said Dr.

Ronald Duman, senior author on the project. "Moreover, the increase in synaptic connections reverses the deficit caused by stress and depression and thereby reinstates the normal control of mood and emotion."

"It would be very important to know if all of the new generation of rapidly acting antidepressant medications acted through a final common signaling pathway within neurons. This knowledge might guide insights into why some patients fail to respond to available antidepressants and provide directions for treating depression," said Dr. John Krystal, Editor of Biological Psychiatry.

The authors agree, noting that these findings suggest that different muscarinic acetylcholine receptor antagonist may be even more effective and cause fewer side effects than scopolamine. Further studies of such agents are already underway.

More information: "Scopolamine Rapidly Increases Mammalian Target of Rapamycin Complex 1 Signaling, Synaptogenesis, and Antidepressant Behavioral Responses" by Bhavya Voleti, Andrea Navarria, Rong-Jian Liu, Mounira Banasr, Nanxin Li, Rose Terwilliger, Gerard Sanacora, Tore Eid, George Aghajanian, and Ronald S. Duman (DOI: 10.1016/j.biopsych.2013.04.025). The article appears in *Biological Psychiatry*, Volume 74, Issue 10 (November 15, 2013)

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