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New Insight Into the Mechanisms of Fast-Acting Antidepressants: What We Learn From Scopolamine

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For a depressed patient, a single day without symptom improvement means yet another day of suffering. The currently available antidepressants require weeks or months to achieve appreciable symptom remission and remain ineffective in a large number of patients. Severely depressed patients are at high risk of suicide, making delayed symptom improvement a life-threatening unresolved problem in psychiatry. Therefore, there is an urgent need to develop new strategies to treat depression more rapidly and more effectively to achieve fast and sustained symptom relief. Research in this area has led to the discovery of the fast-acting antidepressant properties of subanesthetic doses of ketamine, a noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist. In addition, the muscarinic receptor antagonist scopolamine has received attention because it exerts rapid antidepressant effects that may not be directly dependent on NMDAR antagonism (1). Rapid antidepressant effects can be achieved within 2 hours in the case of ketamine or 3 days in the case of scopolamine. These antidepressant effects last for around 1 week and can be prolonged using repeated administration, even in otherwise treatment-resistant patients. However, fast-acting antidepressants have many side effects, including acute dissociative and psychotomimetic properties, a high potential for abuse, and respiratory and cardiovascular problems (2). Considering these safety concerns, refining our understanding of the cellular and molecular mechanisms underlying rapid antidepressant effects will be important to identify new targets for safer and more effective treatments.

In this issue of *Biological Psychiatry*, Ghosal *et al.* (3) set out to determine whether common signaling mechanisms can be identified between scopolamine and ketamine that could lead to the discovery of new targets for improved and safer rapid-acting antidepressants. A well-established mediator of antidepressant responses to fast-acting and typical mono-aminergic antidepressants is brain-derived neurotrophic factor (BDNF). The role of BDNF in fast antidepressant action is supported by studies showing that human carriers of the BDNF Val66Met polymorphism and BDNF Val/Met knock-in mice (4) are resistant to the rapid antidepressant effects of ketamine (5). In the current study in mice, Ghosal *et al.* (3) report that three injections of scopolamine over the course of 5 days reduces immobility in the forced swim test and decreases the latency to feed in the novelty suppressed feeding test—measures of depression- and anxiety-like behavior, respectively. Similar to ketamine, the antidepressant effects of scopolamine were absent in BDNF Val/Met mice, which exhibit

altered BDNF trafficking and reduced activity-dependent BDNF release. These data demonstrate that the activity-dependent release of BDNF may indeed be a molecular convergence point for both drugs.

To gain insight into the neural circuitry involved in the rapid antidepressant effects of scopolamine, Ghosal *et al.* (3) then investigated the effects of scopolamine in the prefrontal cortex (PFC), a brain region known to mediate the fast antidepressant responses to ketamine (6). They found that scopolamine treatment increased phosphorylation of the cognate receptor for BDNF, tropomyosin receptor kinase B (TrkB), and that infusion of an antibody against BDNF into the PFC blocked the antidepressant effects of scopolamine. These data indicate that BDNF signaling specifically in the PFC is also necessary for the rapid antidepressant action of scopolamine.

BDNF release is a highly regulated process that has been extensively studied within the context of ketamine treatment. Ketamine's noncompetitive antagonism at the NMDAR on inhibitory gamma-aminobutyric acidergic (GABAergic) interneurons in the PFC results in decreased GABA release and subsequent disinhibition of glutamatergic neurons (7). This "burst" in glutamate release then activates alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA) and L-type voltage-dependent calcium channels on the postsynaptic membrane, leading to increased firing of the postsynaptic neuron and the activity-dependent release of BDNF. The synaptically available BDNF then binds to the tropomyosin receptor kinase B receptor, which gets phosphorylated upon BDNF binding and subsequently activates extracellular signal-regulated kinase 1/2 and protein kinase B. These kinases then phosphorylate the mammalian target of rapamycin (mTOR), which activates its downstream target p70 S6 kinase. Finally, p70 S6 kinase promotes synaptogenesis by increasing translation of the synaptic proteins GluR1 and PSD95 (Figure 1).

Previous research from Voleti *et al.* (8) had shown that, similar to ketamine, scopolamine also activates AMPARs and stimulates mTORC1 signaling in the PFC, including phosphorylation of protein kinase B, mTOR, and p70 S6 kinase. In the present study, Ghosal *et al.* (3) report that blocking voltage-dependent calcium channels also counteracts the scopolamine-induced activation of mTORC1 signaling in the PFC and blocks the rapid antidepressant effects of scopolamine in the forced swim test and novelty suppressed feeding test. These findings extend our understanding of fast-onset antidepressant mechanisms by demonstrating that the same elements of the mTORC1 signaling pathway are used by both scopolamine and ketamine in the PFC.

To investigate the direct effects of scopolamine on BDNF signaling at the cellular level, the authors complemented their *in vivo* studies with primary rat cortical cell cultures that contain glutamatergic, GABAergic, and cholinergic neurons to model the cellular interactions in the PFC *in vitro*. The authors show that BDNF release from cultured cortical cells is dependent on both AMPAR and voltage-dependent calcium channel activation and that BDNF dose-dependently increases extracellular signal-regulated kinase 1/2 phosphorylation via a tropomyosin receptor kinase B-dependent mechanism. Scopolamine also increased the dendritic complexity of cultured cortical neurons, and these synaptogenic effects have indeed been proposed to be underlying the rapid behavioral effects of fast-acting

antidepressants (6). Interestingly, BDNF release was blocked by the GABA_A receptor agonist muscimol. This finding supports the notion that, similar to ketamine, blocking GABAergic inhibition onto glutamate neurons may initiate the activity-dependent BDNF release, and subsequently activate mTORC1 signaling in these cells (Figure 1).

But how can scopolamine, a nonselective muscarinic receptor antagonist, exert similar effects as the noncompetitive NMDAR antagonist ketamine? Muscarinic receptors M1 to M5 are G protein-coupled receptors with diverse effects on intracellular signaling pathways and on neuronal activity. Determining exactly which muscarinic receptor is responsible for scopolamine's action before AMPARs are activated and BDNF is released will be important to understand how scopolamine initiates the same signaling cascade as ketamine that ultimately leads to mTORC1 activation and enhanced synaptogenesis. Navarria *et al.* (9) previously showed that the selective M1 antagonist VU0255035 produces antidepressant effects and stimulates mTORC1 signaling in vivo. In the current study, Ghosal *et al.* (3) found that similar to scopolamine, the M1 antagonist VU0255035 increases AMPA-dependent BDNF release and activates mTORC1 signaling in cultured cortical neurons in vitro. Taken together, these findings suggest that by blocking the M1-mediated excitatory effects of acetylcholine on GABAergic interneurons, scopolamine may disinhibit glutamate release, enhance AMPAR stimulation, and produce downstream effects similar to that of ketamine (Figure 1). Future studies using selective antagonists against each individual muscarinic receptor will be needed to fully elucidate their value as novel targets for rapid and safe antidepressants.

The findings of Ghosal *et al.* (3) advance our understanding of fast-onset antidepressant action in several important ways. First, their study finds substantial convergence between the molecular mechanisms of scopolamine and ketamine, while also providing insight into the different entry points used by these two drugs (i.e., M1 antagonism vs. NMDAR antagonism, respectively). These common molecular pathways may be promising targets for improved rapid-acting antidepressants with safer side effect profiles. While mTOR-dependent synapse formation in the PFC has been shown to be crucial for rapid antidepressant effects (6), it is important to keep in mind that the PFC is integrated into highly organized neural circuits with other brain regions involved in mood regulation. These regions include, for example, the hippocampus, nucleus accumbens, the hypothalamus, the amygdala, and the ventral tegmental area, all of which have been implicated in mood and anxiety, as well as in the therapeutic response to typical antidepressants (10). How these brain regions and different functional cell types within these regions are affected by rapid antidepressants will be a challenge for future studies and for the development of new antidepressants.

Finding new treatment strategies to confer fast antidepressant effects is a priority in psychiatric research, and Ghosal *et al.* (3) bring us one step closer to achieving this goal. The second but no less important challenge is to achieve sustained symptom remission. Identifying intersections between the cellular and molecular mechanisms that confer rapid and long-lasting antidepressant effects could potentially lead to new treatments to achieve both. One such intersect is the common effect on neuroplasticity. By combining strategies that acutely increase synaptogenesis to confer rapid effects, while at the same time

increasing neurogenesis for sustained remission, may be promising new research avenues to pursue (10).

Scopolamine and ketamine are currently infused intravenously in a clinical setting for approximately 40 minutes, and the severe side effects need to be monitored closely by appropriately trained clinicians. New treatments will ideally need to be developed so they can be easily administered at home without the need for a clinical setting. Improving the safety profile and reducing their abuse potential will be crucial before such drugs become reality.

These are exciting times for research into rapid-acting antidepressant mechanisms, which might yield important leads for developing new treatments for depression. Targeting molecular mechanisms to achieve both rapid symptom improvement and sustained effects by counteracting neural circuit dysfunction in depression will be a promising approach to develop new and improved antidepressant therapies.

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References

1. Furey ML, Drevets WC (2006): Antidepressant efficacy of the anti-muscarinic drug scopolamine: A randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* 63:1121–1129. [PubMed: 17015814]
2. Sanacora G, Frye MA, McDonald W, Mathew SJ, Turner MS, Schatzberg AF, et al. (2017): A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry* 74:399–405. [PubMed: 28249076]
3. Ghosal S, Bang E, Yue W, Hare BD, Lepack AE, Girgenti MJ, Duman RS (2018): Activity-dependent brain-derived neurotrophic factor release is required for the rapid antidepressant actions of scopolamine. *Biol Psychiatry* 83:29–37. [PubMed: 28751069]
4. Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, et al. (2006): Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science* 314:140–143. [PubMed: 17023662]
5. Laje G, Lally N, Mathews D, Brutsche N, Chemerinski A, Akula N, et al. (2012): Brain-derived neurotrophic factor Val66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. *Biol Psychiatry* 72:e27–e28. [PubMed: 22771240]
6. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. (2010): mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329:959–964. [PubMed: 20724638]
7. Wohleb ES, Wu M, Gerhard DM, Taylor SR, Picciotto MR, Alreja M, Duman RS (2016): GABA interneurons mediate the rapid antidepressant-like effects of scopolamine. *J Clin Invest* 126:2482–2494. [PubMed: 27270172]
8. Voleti B, Navarria A, Liu RJ, Banasr M, Li N, Terwilliger R, et al. (2013): Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. *Biol Psychiatry* 74:742–749. [PubMed: 23751205]

9. Navarria A, Wohleb ES, Voleti B, Ota KT, Dutheil S, Lepack AE, et al. (2015): Rapid antidepressant actions of scopolamine: Role of medial prefrontal cortex and M1-subtype muscarinic acetylcholine receptors. *Neurobiol Dis* 82:254–261. [PubMed: 26102021]
10. Anacker C, Hen R (2017): Adult hippocampal neurogenesis and cognitive flexibility - linking memory and mood. *Nat Rev Neurosci* 18:335–346. [PubMed: 28469276]

Figure 1.

Schematic representation of the converging signaling pathways of scopolamine and ketamine in the prefrontal cortex. **(A)** Activation of M1 muscarinic receptors on gamma-aminobutyric acidergic (GABAergic) interneurons by acetylcholine (ACh) activates intracellular G_q-proteins, which activate phospholipase C (PLC), which in turn converts phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerol and inositol-1,4,5-trisphosphate (IP3). IP3 then binds to IP3 receptor calcium (Ca²⁺) channels on the endoplasmic reticulum, allowing Ca²⁺ to be released from intracellular stores into the

cytoplasm. Activation of *N*-methyl-D-aspartate (NMDA) receptors by glutamate causes Ca^{2+} influx through the cell membrane. Elevated intracellular Ca^{2+} concentrations increase neuronal activity and firing of GABAergic interneurons, leading to GABA release into the synaptic cleft. GABA activates GABA_A receptors, thereby inhibiting glutamatergic neurons through membrane hyperpolarization. **(B)** Scopolamine blocks M1 receptors on GABAergic interneurons; ketamine blocks NMDA receptors. In both cases, intracellular Ca^{2+} levels are decreased in GABAergic interneurons, which reduces GABA release and blocks the GABA_A -mediated inhibition of glutamatergic neurons. As a result, more glutamate can be released to activate postsynaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (“glutamate burst”). Activation of AMPA receptors by glutamate causes Ca^{2+} influx and subsequent activation of L-type voltage-dependent calcium channels (VDCCs), leading to increased intracellular Ca^{2+} levels of the postsynaptic neuron and activity-dependent release of brain-derived neurotrophic factor (BDNF) into the synaptic cleft. BDNF then binds to its cognate tropomyosin receptor kinase B (TrkB) receptor, leading to TrkB phosphorylation and activation. TrkB then activates extracellular signal-regulated kinase 1/2 (ERK 1/2) and protein kinase B (Akt) through phosphorylation. ERK 1/2 and Akt in turn phosphorylate the mammalian target of rapamycin (mTOR), which phosphorylates its downstream target p70 S6 kinase (S6K). S6K increases translation of the synaptic proteins GluR1 and PSD95, which promote synaptogenesis. Na^+ , sodium.