

Current drug development for antidepressants and ideas addressing downstream glutamate: the ketamine example

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Novel antidepressant drug development remains an elusive goal despite tests of scores of agents with molecular mechanisms that go beyond those involved in the action of currently marketed antidepressants. Clinical trials of agents with supposedly promising novel mechanisms for treating symptoms of depression have been followed by disappointing, clinically insignificant results in Phase 2 or Phase 3. It is unclear, however, how many of these studies provide interpretable data that rule out a specific mechanism of antidepressant action. With current technologies, we are now able to test many hypotheses by assuring ourselves that we have target engagement and downstream functional activity in the brain. The expectation is that application of these measures will allow us to at the very least rule out mechanisms more quickly than previously.

The replication of transient antidepressant effects of intravenous (iv) ketamine in patients who do not respond to marketed antidepressants provides hope of identifying a truly useful novel therapeutic mechanism.^{1,2} Scopolamine, too, is now reported to have acute antidepressant effects. Our focus here, however, is to emphasize how one might go about exploring the therapeutic potential of a single compound and understanding the mechanism by which it works. For ketamine, that focus is on glutamate, which has long been recognized to have great antidepressant potential.^{3,4} The mechanisms by which ketamine exerts its therapeutic effects as a rapid-acting antidepressant are not understood, because both its pharmacologic properties in humans and the clinical syndrome on which it operates are poorly understood. The task is to relate a specific property or properties for ketamine to specific

and well-defined quantitative biochemical or physiological measures in patients that go beyond traditional clinical severity ratings.

The challenge is potentially greater when we focus on “treatment-resistant” subpopulations, which likely encompass multiple pathophysiological states. We believe that a primary issue in terms of moving beyond currently available antidepressants is using the syndromal major depressive disorder (MDD) diagnosis, which has been applied in large multisite trials as the sole basis for selecting subjects to be treated with novel agents. So, rather than conceptualize MDD or treatment-resistant depression as syndromes with 1 or 2 primary etiologies, we can now focus on more specific domains in which function is disrupted. This goes beyond the simple analogy of modifying the experience of pain independent of etiology to recognizing that different pathways mediate components of pain and that one might selectively interfere at a number of levels to provide benefit. We take “anhedonia” as an example. Classically, in depression, there is a dramatic decrease in the ability to experience pleasure or gratification. Contemporary neuroscience has developed ways of measuring events in certain brain regions that are involved in reward behavior both in animals and humans.⁵ This provides an opportunity to identify humans who are at the low end of the reward pathway response and to test whether specific agents can increase these brain responses. In turn, one can see if increased brain responses are associated with people reporting and showing increased pleasurable experiences.

Relating a clinical domain to a circuit that can be interrogated in humans and models provides a possible approach to explore the role of glutamate in “antidepressant” action. Thus, given the diffuse role of this excitatory amino acid, one could seek a defined domain of behavior linked to a brain circuit that can be up- or

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down-regulated by a specific glutamate receptor agent. Ketamine has long been of interest outside of its use as a “dissociative anesthetic” to induce altered states in humans that are seen as mimicking components of psychosis as well as producing other disturbances of cognitive function. Thus, when investigating the brain effects of ketamine in humans, investigators focus on regions of interest that are believed to be relevant to psychosis in schizophrenia. Some recent studies following areas of increased functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) signal after ketamine have taken a more agnostic approach of simply looking at the areas that show the largest and/or most reproducible increases in healthy volunteers.⁶ The purpose of these studies is to use blockade of any ketamine signal as evidence of drug action in the brain with clinical doses of both risperidone and lamotrigine. Interestingly, there is no evidence that the antiepileptic lamotrigine is an antipsychotic, so direct inferences on clinical application do not follow from reversing effects of ketamine on a specific brain area. Lamotrigine does show beneficial effects in patients with bipolar depression, but whether this action involves the same brain region(s) that are affected by ketamine is unknown.

Ketamine itself poses something of a paradox, whereby it is studied both as a tool to model aspects of psychosis as well as produce acute antidepressant effects. If we approach this puzzle by going more deeply into dissecting the findings touched on above, we believe that further advances are possible with general implications for strategies of novel antidepressant development. A crucial step is to better understand the full range of *in vivo* actions of ketamine at the molecular pharmacological level. Conceptually, the simplest approach is to synthesize highly specific compounds that engage all of the targets that ketamine can be shown to affect. To this end, antagonists of the NR2B subunit of the N-methyl-D-aspartate (NMDA) receptor, which is believed to be a primary site of ketamine action, have been developed and tested in humans. Insufficient data are available to make final conclusions, but the data generated to-date indicate that at doses of ketamine that produce an increase in blood pressure, one does not observe dissociative or, for that matter, antidepressant effects. Alternatively, as suggested in the review by Pehrson and Sanchez,⁷ one could explore selective modulators of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to see if they could reproduce the desired effects of ketamine. An additional strategy is to relate the molecular actions of ketamine to effects on brain circuits in animals as a basis for identifying mechanisms that might generate analogous circuit effects to those that can be evaluated in humans.⁸

Preclinical studies in rodents have begun to look at regional and temporal dynamics of cellular and molecular

events triggered by ketamine to enhance synaptic plasticity in the prefrontal cortex and hippocampus.⁸ The availability of tools to selectively modulate the signaling molecules that are implicated in ketamine’s rapid antidepressant effects (eg, neurotrophic factors, mTOR, eEF2 kinase, GSK-3 β) will enable one to establish a link between the molecular signatures and behavioral effects. These hypotheses can then be tested in human studies with proteomic and other approaches in biofluid samples or patient-derived stem cells.

For instance, were neurotrophic factors found to mediate acute ketamine effects on circuits viewed as most likely linked to antidepressant effects, then one would develop a biomarker of affecting neurotrophic factors in human brain. The next step would be to combine the preclinical study of pharmacodynamic (PD) effects on neurotrophic factors with dose-response studies in healthy subjects to verify that analogous PD effects were achieved and ultimately to establish relationships to clinical effects. A recent review provides detailed examples of such PD approaches.⁹ As our methods of tracking more specific human behavioral domains mature, we can move beyond item analysis of scales developed 50 years ago to more precise measures of overall improvement linked to, for instance, an inability to experience pleasure or an inability to concentrate. From this work it will become possible to articulate a series of testable hypotheses, such as whether engagement of a specific molecular site in the brain produces circuit effects that are tightly linked to dissociative and/or antidepressant effects. It could emerge that the mechanism that generates dissociative effects is the same as the one associated with rapid onset of antidepressant activity. Ideally we will find that compounds can produce the antidepressant effects without the dissociative effects. But if these pharmacologic effects are tightly linked, then one can have an informed discussion on the trade-offs of clinical benefit vs abuse potential of ketamine.

Our expectation is that with the tools now or soon to be available, we can both work “top-down” from clinical findings with poorly understood agents such as ketamine as well as “bottom-up” with agents developed to affect specific molecular targets and circuits that can be interrogated in humans and linked to specific domains that are affected in depression or in other psychiatric conditions. This approach should allow for much more rapid ruling in or out of the potential clinical utility of any single molecular mechanism. We appreciate that there are likely many instances in which more than 1 mechanism must be targeted to achieve clinical effects, as in many fields of medicine, but the experience with highly selective serotonin reuptake inhibitors shows that there remains great potential in single primary action agents. And, to date, large clinical trials fail to convincingly show the broader efficacy of combined action agents, which many believe to be superior whether in the antidepressant or

antipsychotic space. An emerging example is provided by vortioxetine, which, in addition to serotonin transporter reuptake inhibition, which can be established with PET imaging, is speculated to indirectly influence glutamate function through various 5-HT receptors,⁷ a possibility that remains to be demonstrated in humans. We would expect that the same approach we have outlined for better understanding the actions of ketamine could be applied to teasing apart differential effects of single vs such multiple action compounds. That path is longer and more complicated, since it will require understanding the consequences of affecting each pharmacologic mechanism involved and a level of systems neuroscience that is several years away.

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