# Neurobiological advances identify novel antidepressant targets

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It has been over fifty years since the development of monoamine reuptake inhibitor antidepressants, that are widely prescribed and are the medication of choice for the treatment of depressive disorders. Although these agents have been useful, they also have significant limitations, including slow onset of action (weeks to months) and low rates of efficacy (approximately one third of patients respond to initial treatments). Thus, there is a significant unmet need for more effective, rapid-acting agents that have novel mechanisms.

Here we discuss a few selected new areas of drug development and targets that are based on the combination of neurobiological research and clinical findings. This work holds promise for the development of new rapid-acting agents that may enhance the pharmacological armament for the treatment of depression.

## TARGETING THE GLUTAMATERGIC SYSTEM: KETAMINE AND RAPID-ACTING ANTIDEPRESSANTS

Pharmacological agents that regulate glutamate, the major excitatory neurotransmitter in the brain, have been under development for the treatment of nearly every major psychiatric disorder, as well as many neurological conditions, for nearly two decades, but only recently have their potential and impact for treating depression been realized.

This is based largely on studies of ketamine, a glutamatergic N-methyl-d-aspartate (NMDA) receptor antagonist which produces rapid (within hours) antidepressant effects in treatment resistant depressed patients (1), representing one of the most significant discoveries in the field of depression since the introduction of the monoamine reuptake inhibitors. This important clinical finding has stimulated subsequent studies of the neurobiological mechanisms underlying the actions of ketamine, which have provided a number of targets for development of new antidepressant medications that are more selective and that have fewer side effects than ketamine.

The most notable ketamine-related targets are found within the glutamate neurotransmitter system (2). Through blockade of NMDA receptors, ketamine causes a rapid, transient increase of extracellular glutamate in the prefrontal cortex (PFC), and its antidepressant actions are blocked by pre-treatment with a glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist (2,3). The "burst" of glutamate caused by ketamine is thought to occur via disinhibition of tonic firing GABAergic interneurons, causing increased glutamate neurotransmission (4). The increase in glutamate activity is accompanied by an increase in the number and function of spine synapses and rapid reversal of the effects of chronic stress (3). Moreover, ketamine stimulates the mammalian target of rapamycin (mTOR), a signaling system that controls the translation of synaptic proteins. Importantly, the synaptogenic and behavioral actions of ketamine are blocked by infusion of a selective inhibitor of mTOR, demonstrating a requirement for this signaling pathway (3). These effects are thought to underlie the antidepressant actions of ketamine by blocking or reversing the synaptic connection deficits caused by stress and depression, thereby reinstating normal control of mood and emotion (2).

Based on these studies of ketamine, several antidepressant targets have been identified within the glutamate system.

First, there is evidence that NR2B is the relevant receptor subtype that mediates the actions of ketamine. Basic research studies demonstrate that the NR2B selective antagonist Ro 25-6981 also produces rapid antidepressant behavioral effects, increases mTOR signaling, and increases synaptic proteins in the PFC (3). There is also preliminary evidence that the NR2B selective antagonist CP-101,606 produces rapid antidepressant effects in depressed subjects, although not as rapidly as ketamine (2).

Second, the presynaptic glutamate autoreceptors, the metabotropic glutamate receptor 2/3 (mGluR2/3) subtypes, are a likely target, as blockade of these receptors controls the release of glutamate. This hypothesis is supported by studies demonstrating that mGluR2/3 antagonists (LY341495 and MGS0039) produce rapid antidepressant actions in behavioral models, including the forced swim test (2). LY341495 also produces a rapid response in a chronic unpredictable stress-anhedonia paradigm, considered one of the best models of depression, and one of the most rigorous for testing rapid-acting agents, as typical antidepressants are only effective after chronic (3 weeks) treatment in this paradigm (5). The possibility that these agents are acting through mechanisms similar to ketamine is supported by evidence that mGluR2/3 antagonist treatment increases mTOR signaling in the PFC, and the antidepressant behavioral effects are blocked by pretreatment with a selective mTOR inhibitor.

Third, based on evidence that ketamine increases glutamate and that the behavioral effects are blocked by an AMPA receptor antagonist, agents that act as AMPA

receptor potentiators could also have antidepressant efficacy. These drugs have been developed for use as cognitive enhancers and are reported to have efficacy in models of depression (2). Further studies are needed to determine if AMPA potentiators, as well as NR2B and mGluR2/3 antagonists, produce a rapid induction of synaptic connections in rodent models, and ultimately to determine their clinical efficacy in depressed patients.

## OTHER KETAMINE-RELATED TARGETS

Studies of ketamine and other rapid-acting agents have identified additional targets for drug development.

One is brain derived neurotrophic factor (BDNF), which plays an important role in the survival of neurons in the adult brain, as well as in neuroplasticity and synaptogenic responses in models of learning and memory. Basic research studies demonstrate that the behavioral actions of ketamine are blocked in BDNF mutant mice, including mice which carry a human polymorphism, Val66Met, that blocks the release of BDNF (2). This has resulted in clinical studies reporting that depressed patients with the BDNF Met allele have a significantly reduced response to ketamine. These studies also indicate that a BDNF agonist could produce rapid and efficacious antidepressant actions, although development of small molecule BDNF agonists has not been successful to date.

Another target that has been identified in studies of ketamine is glycogen synthase kinase-3 (GSK-3). This work demonstrates that the antidepressant effects of ketamine do not occur in mice with a GSK-3 mutation that blocks ketamine-induced phosphorylation and inhibition of this kinase (2). This suggests that a GSK-3 inhibitor would produce rapid antidepressant actions in behavioral models, although additional studies to rigorously test this hypothesis in chronic models are needed. In addition, there is new evidence that the combination of a low dose of ketamine and lithium, a GSK-3 inhibitor, produces an additive antidepressant and synaptogenic response, and similar effects are observed with a selective GSK-3 inhibitor (6). These findings indicate that lower and safer doses of ketamine, when combined with lithium, could be used for the rapid and sustained treatment of depression. It is also possible that lithium or another GSK-3 inhibitor could sustain the actions of ketamine, beyond the 1 to 2 weeks typically seen before relapse in depressed patients.

In addition to ketamine, there is evidence that scopolamine, a non-selective muscarinic receptor antagonist, also produces rapid antidepressant actions in depressed patients (7). Basic research studies demonstrate that scopolamine also increases mTOR signaling and synaptogenesis in PFC, and that the behavioral actions of scopolamine are blocked by either an AMPA receptor antagonist or a selective mTOR inhibitor (8). These studies also demonstrate that scopolamine increases extracellular glutamate in PFC. Together with the studies of ketamine, these findings indicate a common pathway for rapid acting antidepressants. Studies are currently underway to identify which of the five muscarinic receptor subtypes mediate the effects of scopolamine, thereby providing a target for development of a selective antagonist with fewer side effects than scopolamine.

## INFLAMMASOME AND PRO-INFLAMMATORY CYTOKINES

Another emerging area of interest is inflammation and blockade of pro-inflammatory cytokines. There are consistent reports of elevated levels of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), IL-6 and tumor necrosis factor-alpha (TNF-α), in depressed patients (9). Moreover, basic research studies have begun to elucidate the inflammation processes that underlie the synthesis and release of these cytokines. These studies demonstrate that stress increases the synthesis and release of pro-IL-1β, IL-6, and TNF-α in brain microglia, as well as the processing of pro-IL-1β to the mature form via activation of caspase-1 (9). The latter step involves stimulation of a purinergic receptor, P2X7, located on microglia and macrophages, which leads to activation of the inflammasome and pro-caspase-1.

The potential role of pro-inflammatory cytokines in depression is supported by several lines of evidence from basic research studies (9). First, administration of an IL-1β antagonist or neutralizing antibody produces an antidepressant effect in a chronic stress-induced anhedonia model. Second, administration of a P2X7 receptor antagonist also produces an antidepressant response in the chronic stress model, as well as other standard antidepressant and anxiety paradigms. Third, preliminary studies demonstrate that mice with a mutation of one of the key inflammasome components (NLRP3) are resilient to the effects of chronic stress (9).

The potential impact of this new area of research is further highlighted by the evidence that the inflammasome and pro-inflammatory cytokines are involved in metabolic (diabetes) and cardiovascular diseases that have high rates of comorbidity with depression. These findings suggest that the inflammasome-pro-inflammatory cytokines may represent a common nexus for stress, cardiovascular disease, and metabolic imbalances that underlie or contribute to these comorbid illnesses.

## FUTURE DIRECTIONS

The new depression related targets identified by studies of rapid-acting antidepressants and pro-inflammatory cytokines are cause for optimism for new, rapid, and more effective treatments with novel mechanisms. New targets are likely to be revealed by further studies of the neurobiological

mechanisms underlying depression and treatment response. Major advances are being made at a fast pace using a variety of new techniques, such as optogenetic stimulation of neural circuits, and methods for sophisticated tracking of the connectome that underlies mood disorders (10,11).

Together these studies provide elegant approaches to identify the specific subsets of neurons that produce antidepressant effects in rodent models, as well as the extended circuits that underlie these effects. This will lead to further characterization of the neurotransmitter systems and intracellular signaling pathways that regulate these neurons and circuits, and thereby provide new targets for development of antidepressant medications that can normalize these disrupted depression pathways.

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