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Neurobiology of Rapid Acting Antidepressants: Role of BDNF and GSK-3β

Recent studies demonstrate that a single dose of ketamine, a glutamate NMDA receptor antagonist, produces rapid antidepressant actions in treatment-resistant patients, one of the most significant advances in the field of depression in recent years. Preclinical studies demonstrate that the rapid antidepressant actions of ketamine are mediated by the induction of synaptic proteins and increased number and function of new spine synapses in the prefrontal cortex (PFC; Duman and Aghajanian, 2012). In addition, the behavioral and synaptogenic effects of ketamine require brain-derived neurotrophic factor (BDNF) and stimulation of the mechanistic target of rapamycin complex 1 (mTORC1), which is involved in protein synthesis-dependent synaptic plasticity. Surprisingly, we have also found that scopolamine, a muscarinic receptor antagonist that produces rapid antidepressant effects, also increases mTORC1 and induces synaptogenesis in the PFC (Voleti *et al*, 2013).

Although ketamine is an NMDA receptor antagonist, it paradoxically increases glutamate transmission in the PFC. This is thought to occur via blockade of tonic firing GABAergic interneurons, resulting in disinhibition of glutamate release. The resulting 'burst of glutamate' contributes to activity-dependent release of BDNF and increased synaptogenesis (Duman and Aghajanian, 2012). A functional BDNF polymorphism, Val66Met, has provided an approach to examine the role of BDNF in depressed patients, as well as rodent models. We have found that the rapid actions of ketamine are blocked in mice with a knockin of the Met allele, which prevents the processing and release of BDNF (Liu *et al*, 2012). Moreover, depressed patients who are carriers of the Met allele show a significantly decreased response to ketamine, indicating that the Met allele is a marker of nonresponders (Laje *et al*, 2012).

Another interesting update is related to the finding that the actions of ketamine require inhibition of glycogen synthase kinase-3β (GSK-3β) Beurel *et al*, 2011), a protein kinase implicated in the pathophysiology and treatment of depression and bipolar disorder. We have found that lithium or a selective GSK-3β inhibitor significantly enhances the effects of a low dose of ketamine (Liu *et al*, 2013), raising the possibility that a low-dose ketamine + lithium combination could be repeated with reduced risk of side effects.

The ketamine studies highlight several novel concepts for the development of efficacious, rapid acting, and safe medications. First, ketamine and its acute actions (eg, the burst of glutamate) are transient (1–2 h), which avoids excitoxic damage; this differs from traditional approaches to develop long-lasting pharmacological agents. Second, in contrast to traditional approaches, one of the core pathophysiological changes underlying major depression—a loss of synaptic connectivity—is rapidly addressed. Third, the increased synaptic connections induced by a single dose of ketamine are long-lasting (7–10 days), indicating that it is possible to stimulate therapeutic adaptations that outlast the initial drug actions. In addition, preliminary studies demonstrate that ketamine can enhance other behaviors that require learning and synaptogenesis, notably the extinction of fear conditioning (unpublished). Together these studies demonstrate that ketamine produces rapid remodeling of synapses that control mood and emotion in the treatment of depression, and the feasibility of utilizing similar remodeling approaches for the treatment of other illnesses, such as PTSD.

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Seeing the Future: Epigenetic Biomarkers of Postpartum Depression

Postpartum depression (PPD) affects between 10 and 20% of women in the general population, but the risk is much higher in women with a history of major depression (MDD) or bipolar