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## Neurobiology of Rapid Acting Antidepressants: Role of BDNF and GSK-3$\beta$

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-3$\beta$ (GSK-3$\beta$) 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-3$\beta$ 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

disorder (BP) with at least 30% developing PPD (Payne *et al*, 2007). There is evidence that women with a history of PPD are affectively susceptible to hormonal change: Bloch *et al* (2000) demonstrated that women with a history of PPD developed mood symptoms in response to a blinded withdrawal of supraphysiological levels of estrogen and progesterone compared to none of controls.

We used a cross-species translational design to identify estrogen-mediated epigenetic changes associated with PPD (Guintivano *et al*, 2013). DNA methylation profiles were generated from whole blood using methylation microarrays in a sample of PPD high-risk women who were followed prospectively through pregnancy and after delivery. These profiles were cross-referenced with syntenic locations, which demonstrated murine hippocampal DNA methylation changes in response to long-term treatment with 17β-estradiol (E2). Initially, we investigated only DSM-4 defined PPD where women suffered a major depressive episode within 4 weeks of delivery. Using this group, we identified two biomarker loci at *HP1BP3* and *TTC9B,* which predicted PPD with an area under the receiver operator characteristic curve (AUC) of 0.87. In a replication analysis, these biomarkers also functioned to segregate PPD status in women who developed depression during the antenatal period with 88% accuracy; however intriguingly, the prediction was in the opposite direction. There is controversy in the literature as to whether PPD as defined by DSM-4 is a unique entity from depression that begins during pregnancy and continues postpartum. In light of previous reports demonstrating depression-associated changes in white blood cell type compositions (Lutgendorf *et al*, 2008), we compared the two groups and found a decrease in the ratio of monocytes to lymphocytes and granulocytes in the antenatally depressed women that correlated with *HP1BP3* DNA methylation status. Incorporation of cellular composition into the model enabled a prediction of PPD status with an AUC of 82% independent of antenatal depression status.

Our results further suggested that there is an enhanced sensitivity to estrogen-based DNA methylation reprogramming in the hippocampus in those at risk for PPD, independent of antenatal depression status. Our findings are consistent with the hypotheses of hormone sensitivity-mediated PPD risk put forth by Bloch *et al*, as well as previous work implicating an increased sensitivity of the stress system with antenatal depression (Katz *et al*, 2012).

As estrogen is closely tied to both the hypothalamic pituitary adrenal (HPA) axis as well as inflammation, it is conceivable that our findings represent a first step in unifying the disparate definitions of PPD into a common etiology of estrogen sensitivity and possibly a continuum of vulnerability to its downstream consequences. Whether our identified biomarkers represent a mere proxy of estrogen sensitivity or are involved in PPD pathophysiology will require further study. *TTC9B* may be linked to regulation of AMPA receptor levels, which in turn have been shown to be associated with resilience or vulnerability to stress (Schmidt *et al*, 2010). If the molecular changes exhibited by the biomarkers indicate a biological vulnerability, these may interact with stress occurring in the postnatal period and ultimately lead to depression. The use of animal models to either alter brain biomarker expression or to simulate hormone sensitivity differences may be used to test these mechanistic hypotheses. Further research will be needed to determine whether the identified biomarkers will display PPD predictive alterations at periods of low circulating estrogen in non-pregnant women; however, as high estrogen levels are a feature of normal pregnancy, these biomarkers are capable of early screening for PPD during pregnancy independent of whether they represent trait or state biological variation.

In conclusion, we have identified biomarkers for postpartum mood status that correctly identify whether or not a woman will be depressed during the postpartum time period, regardless of whether or not she is depressed during pregnancy. Future work is needed to confirm these findings and to determine whether identification of women at risk will allow successful prevention of PPD.

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ZK and JP co-inventors listed on a patent application for DNA methylation at biomarker loci related to PPD. In the past year, JP has conducted consulting work for Astra Zeneca and Johnson and Johnson. JP also has a grant from Corcept Pharmaceuticals.

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