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N-Methyl-D-Aspartate Receptors, Ketamine, and Rett Syndrome: Something Special on the Road to Treatments?

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In 2007, Adrian Bird and his colleagues at the University of Edinburgh published a groundbreaking study demonstrating that Rett syndrome (RTT), a severe genetic neurodevelopmental disorder, is reversible in mouse models of the disease (1). Using Cre-Lox technology, the Bird group engineered a mouse in which the disease-causing gene, *Mecp2*, could be reversibly inactivated. Animals born with the gene switched off —a condition that mimics the loss of *MECP2* function that underlies the human disease— developed full-blown symptoms of murine RTT. However, when the gene was reactivated in these severely ill mice, neurological dysfunction was reversed to a significant degree. This remarkable finding demonstrated that even prolonged loss of *Mecp2* function does not lead to irreversible changes in brain structure or function, consistent with postmortem studies demonstrating the absence of neuronal cell loss or neurodegeneration in RTT patients. Against the backdrop of these encouraging results, there has been a flurry of activity in recent years to develop pharmacologic interventions that could achieve what Bird's group had accomplished through genetic engineering in mice, i.e., symptom reversal in RTT.

RTT is a complex and devastating disorder affecting approximately 1 in 10,000 female individuals worldwide. The complexity of RTT derives from the fact that *MECP2* encodes a highly abundant DNA binding protein that influences the expression of many downstream genes and signaling pathways, particularly in the brain. Because *MECP2* is an X-linked gene and most disease-causing mutations arise in the father's germ line, the vast majority of RTT patients are female heterozygotes who are mosaic for normal and mutant *MECP2*. Once the disorder is fully manifest, which usually occurs within the first few years after birth, patients present with severe abnormalities in motor, respiratory, and autonomic control; loss of speech; increased risk of seizures; and musculoskeletal problems. During early stages of the disease, affected individuals can exhibit autistic-like behaviors, including social withdrawal,

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Disclosures

David Katz serves on the Scientific Advisory Board of the Rett Syndrome Research Trust, has been a consultant for SAGE Therapeutics during the past year, and is a founding advisor to ArRETT Neurosciences, a company seeking to develop treatments for Rett syndrome. Frank Menniti is founder, former Chief Scientific Officer, and stockholder of Mnemosyne Pharmaceuticals, Inc. (now Luc Therapeutics), which is developing *N*-methyl-Daspartate receptor modulators to treat diseases of the central nervous system. Robert J. "Joe" Mather has ownership interest in AstraZeneca, a pharmaceutical company developing *N*-methyl-D-aspartate receptor modulators for the treatment of central nervous system disorders.

which often diminish within a few years. Currently, there are no treatments that ameliorate the pathological effects of *MECP2* disruption in RTT, and the burden of care for affected families is enormous.

One class of molecules that has shown promise in preclinical models of RTT is channel-blocking *N*-methyl-D-aspartate receptor (NMDAR) antagonists. Interest in the NMDAR as a therapeutic target in RTT arose from several lines of investigation, beginning with evidence that loss of *MECP2* function may result in developmental dysregulation of NMDAR expression [reviewed in Katz *et al.* (2)]. In 2012, Kron *et al.* (3) demonstrated that treatment of heterozygous female *Mecp2* mutant mice with a subanesthetic dose of ketamine (8 mg/kg) is highly effective at acutely reversing disease phenotypes, including abnormal patterns of neuronal activation in cortical and subcortical structures as well as sensorimotor dysfunction. Recently, another NMDAR channel blocker, of the low-trapping class, was also found effective at ameliorating symptoms in female RTT mice (4), strengthening the case for a therapeutic benefit of NMDAR antagonism.

In this issue, Mierau *et al.* (5) and Patrizi *et al.* (6) provide further evidence for dysregulation of NMDAR expression (5) and the therapeutic potential of ketamine (6) in mouse models of RTT. Previously, the Fagiolini laboratory reported that loss of *Mecp2* is associated with hyperinnervation of pyramidal neurons by gamma-aminobutyric acidergic inhibitory interneurons in visual cortex and postweaning regression in visual acuity. This was accompanied by a shift in the balance of expression in two NMDAR subunits, GluN2A and GluN2B, toward increased GluN2A (7). During development, GluN2B is expressed first during synapse and circuit formation, followed by expression of GluN2A as circuits and synapses stabilize (8). Significantly, rebalancing GluN2A/GluN2B by genetic reduction in GluN2A expression ameliorated the visual acuity regression in the *Mecp2* knockout mice, strongly implicating NMDAR dysfunction in this RTT phenotype (7). The elegant study by Mierau *et al.* (5) builds on these observations to demonstrate that loss of *Mecp2* disrupts NMDAR subunit expression in visual cortex in a cell-type selective manner. Specifically, the authors show that male mice that are null for *Mecp2* exhibit an acceleration of the normal developmental shift from GluN2B to GluN2A subunits in visual cortical interneurons, whereas, in pyramidal neurons, this shift is retarded. This suggests that the beneficial effect of GluN2A knockdown noted previously (7) may be mediated at the level of cortical interneurons and selective pharmacologic targeting of GluN2A on these interneurons may be a therapeutic strategy. Whether it will be possible to develop cell-type selective GluN2A antagonists is an intriguing question. In addition, it is now clear that NMDAR subunit deployment differs markedly among different brain regions. Whereas visual cortex exhibits a robust developmental shift to a high GluN2A/GluN2B ratio, GluN2B subunits remain highly expressed in the adult prefrontal cortex in rodents and primates, putatively in support of high levels of synaptic plasticity that underlie cognitive functions such as working memory (9). Thus, therapeutic strategies aimed at shifting the balance between GluN2A and GluN2B activity in RTT are likely to impact NMDAR function in different brain regions in different ways, and efforts to develop NMDAR-targeted therapies for RTT will need to take this kind of regional heterogeneity into account. Finally, further studies will be required to understand how these findings in *Mecp2* null male mice will translate to the heterozygous condition that characterizes RTT patients.

In Patrizi *et al.* (6), the authors provide important new information on the therapeutic potential of ketamine in RTT by demonstrating that prolonged treatment of preweaning or postweaning *Mecp2* nulls—with the same subanesthetic dose of ketamine used acutely in the Kron *et al.* study (3) (8 mg/kg) —significantly improves visual cortical function and extends lifespan. Possible improvements in other symptoms, including paw clasping and respiration, were also reported but are less clear, as statistical comparisons among saline- and drug-treated mutants are not described. Of particular importance is that positive treatment effects were measured the day after the last ketamine injection, long after the drug is undetectable in the brain. This indicates that transient NMDAR antagonism is sufficient to sustain improvement in this model. In addition, Patrizi *et al.* (6) provide evidence that prolonged ketamine treatment can ameliorate structural circuit defects that underlie or contribute to neurological dysfunction. Specifically, the authors show that gamma-aminobutyric acidergic hyperinnervation of visual cortical pyramidal neurons is reversed to wildtype levels, concomitant with increased spontaneous and evoked neuronal activity in ketamine-treated *Mecp2* null mice. These findings argue strongly for durability of treatment effects at the level of circuit connectivity. Thus, it now appears that ketamine has beneficial effects in mouse RTT models during both drug-on (3) and drug-off (6) periods, and it will be important to determine which kind of activity may have the greatest therapeutic potential in patients. Toward this end, it will also be important to replicate these findings in *Mecp2* heterozygotes that mimic the somatic mosaicism for normal and mutant MeCP2 that is characteristic of the human disorder.

Potential parallels between the effectiveness of ketamine in mouse models of RTT and major depressive disorder in humans are inescapable, particularly with respect to the possibility of durability of action beyond the acute period of NMDAR antagonism. Trials have already been initiated to test the safety and efficacy of NMDAR antagonists in RTT patients, including dextromethorphan, a weak NMDAR antagonist, and low-dose ketamine [reviewed in Katz *et al.* (2)]. As the RTT field pursues the potential promise of NMDAR antagonists for the treatment of RTT, caution is also warranted, particularly in the case of ketamine. In addition to psychotomimetic risk, there is some evidence, albeit inconsistent, that ketamine may provoke epileptic discharges in some patients with a seizure disorder (10). Whether or not this will be a concern in RTT patients, who are prone to seizures, is currently unknown. Additionally, the Food and Drug Administration guidance for NMDAR-targeted drugs prescribes a series of specialized toxicology studies that need to be conducted in parallel with a drug's clinical development program to establish and document the potential risk of neurotoxicity. Therefore, establishment of minimally effective dose and dosing interval will be critical for progressing NMDAR antagonists into juvenile populations.

Regardless of whether ketamine itself turns out to be a RTT therapeutic, studies such as those highlighted here provide preclinical proof of concept for the ability of NMDAR antagonists to ameliorate neurological dysfunction and reverse at least some circuit-level defects caused by loss of MeCP2. A key step moving forward will be to identify translatable biomarkers of brain function that are improved by treatment with NMDAR antagonists and can be tested in the clinic. The RTT field seems well poised to respond to this challenge, given that ketamine and related molecules have already been shown to improve such end points in RTT mice (2,4,6) and some, such as respiratory function, are being evaluated in

current trials (2). Though much work lies ahead, the progress made thus far in understanding the pathophysiology of RTT and in identifying potential therapeutic targets is truly exciting.

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