Novel Drug Enhances Motor Recovery Following Brain Injury

Every year an estimated 800,000 Americans suffer a stroke. Due to advances in management and awareness, stroke mortality decreased 22% in the past 10 yr. However, it remains a leading cause of long-term disability, reducing mobility in half of stroke survivors over the age 65.1 While serotonergic and dopaminergic pharmaceuticals have demonstrated some promise for post-stroke motor recovery, there is still no therapeutic that is FDA approved for post-stroke motor recovery.2

It has been demonstrated that motor recovery following brain damage is a result of compensatory neural plasticity in intact cortical areas.3 Separately, experience dependent synaptic AMPAR receptor delivery (α-amino-hydroxyl-5-methyl-4-isoxazole-propionic-acid) facilitates learning-based neural plasticity and cortical reorganization following sensory deprivation.4,5 Abe et al6 hypothesized that similar AMPAR activity may facilitate the neural plasticity responsible for motor recovery following brain injury; furthermore, a drug that increases AMPAR delivery may enhance motor recovery.7 They investigated the compound Edonerpic maleate (T-817MA), or EM, based on previous literature that demonstrated the neuroprotective and neurotrophic effects of the compound.8–10 Initially, Abe et al6 found that EM-treated mice had increased AMPAR receptor delivery in the whisker-cortex region compared to vehicle-treated mice. This AMPAR increase was not observed in EM-treated mice when whiskers were removed, indicating that the EM facilitated AMPAR delivery was experience driven. To determine the mechanism behind EM promoted AMPAR delivery, researchers ran neuronal protein lysate through an affinity chromatography comprised of Edonerpic resin, detecting a protein band at 60 kDa. Mass spectrometry unveiled this protein as CRMP2, which was further validated when CRMP2-knockout mice treated with EM failed to express AMPAR receptor delivery. It has been shown that actin depolymerizing factor (ADF)/cofilin mediates AMPAR delivery during neuronal plasticity.11 Through the investigation of Edonerpic-treated long-term-potentiated cortical slices and CRMP2-knockout mice, Abe et al6 demonstrated that EM reacts with CRMP2 to induce ADF/cofilin-mediated AMPAR receptor delivery. After unveiling the EM-AMPAR-CRMP2-ADF/cofilin mechanism, researchers focused on practical applications of EM.

Following confirmation that training mice to reach for food pellets required synaptic AMPAR delivery, investigators induced cortical cryoinjury and administered oral EM (30 mg/kg) or vehicle to mice. After 3 wk from injury, both vehicle and Edonerpic-treated mice were subsequently split again and treated with or without training for the reach task. Mice that received both training and EM performed significantly better than the other 3 groups. There was no significant recovery observed in the other groups. The EM to CRMP-2 mechanism was further validated when treated CRMP-2 knockout mice failed to improve after injury and subsequent training. Investigators reproduced the cryoinjury study above; however, a week after EM mice recovered motor function a second cryoinjury was introduced adjacent to the primary injury. Mice with a second injury lost the once recovered motor function, showing that the EM-mediated motor recovery was a result of peri-injury cortical reorganization.

Since past therapeutics have shown promising results in rodents but failed in primates, Abe et al8 studied the effect of EM in macaque monkeys. The monkeys were trained in simple reach-grasp and the vertical-slit maneuvers, assessing gross and fine motor dexterity, respectively. Internal capsule hemorrhage (ICH) was induced in monkeys via stereotactic elastase injection. After monkeys demonstrated that they could perform 1 post-injury reach, training with or without EM was initiated. The reach-grasp maneuver was assessed in 2 positions: a near reach and a more difficult far reach. EM-treated monkeys recovered significantly faster for both reach locations when compared to vehicle-treated monkeys (P < .001). Performance differences were only significant for the far reach-grasp position at the long-time phase (P < .001). For the vertical-slit fine motor task, EM-treated monkeys recovered significantly faster and demonstrated a more wholesome recovery, with impressive improvements in precision grip and finger-oriented maneuvers (P < .001).

In their prior investigations, the Takahashi lab demonstrated that sensory deprivation led to cortical reorganization via synaptic AMPAR receptor delivery.5 Here they demonstrated that the same receptor plays a key role in rehabilitation-driven cortical reorganization following brain injury and identified the novel pharmaceutical drug target CRMP-2. Furthermore, EM significantly enhanced post-injury AMPAR delivery and rehabilitative functional recovery in mice and primates. Through mass spectrometry, protein affinity chromatography, and studies of potentiated brain slices, Abe et al determined the mechanism behind EM enhanced AMPAR delivery. However, further investigation of EMs effect on serotonergic and dopaminergic pathways and on injury-driven neuroregeneration is warranted. Additionally, animal models testing its efficacy in traumatic brain injury should be conducted. EMs efficacy in various postbrain injury disabilities, such as speech and cognition, should be investigated.

Edonerpic maleate has primarily been studied for its potential applications in
Alzheimer’s disease, though its role in medicine has yet to be elucidated. EM has already passed phase 1 clinical trials, reducing the barrier to clinical application. While a few compounds have shown efficacy in the acute phase of brain injury, EM is the first compound to enhance rehabilitative motor recovery. It is a promising new therapy for patients that have residual motor deficits following various brain injuries including traumatic, ischemic, and hemorrhagic injury. Randomized clinical trials determining its clinical efficacy are likely to follow.

Disclosure
The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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