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Development of Novel Drugs to Promote Functional Recovery After Brain Injury

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Abstract

The central nervous system injury such as stroke can severely cause motor paralysis. Although the approach of rehabilitative training is developed, many patients still face restrictions in their daily living after rehabilitation. Thereby, a new compound with a strong potential to enhance motor function recovery with rehabilitation is an unmet medical need. We focus on the one of glutamate receptors, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which plays an important role in learning and memory. Here, we found a novel small low molecular compound, edonerpic maleate, that facilitated experience-dependent synaptic AMPA receptor delivery in the barrel cortex and dramatically accelerated motor function recovery after brain damage in a rodent model. Furthermore, edonerpic maleate enhanced the upper limb function recovery of macaque monkeys with internal capsule hemorrhage. Currently, a phase 2 clinical trial is being conducted to verify the efficacy of edonerpic maleate in stroke patients and has attracted global attention.

Keywords

AMPA receptors
Brain injury
Functional recovery
Neural plasticity

1. Introduction

Stroke is said to occur in about 300,000 people per year in Japan, and is a cause of motor paralysis due to damage to the corticospinal tract, leading to the need for nursing care. Although rehabilitation after stroke has been developed, more effective treatment methods are still needed. The elucidation of functional recovery mechanisms in post-stroke rehabilitation is considered essential for the development of treatment methods, and in recent years, research papers have been reported that have approached the elucidation of functional recovery mechanisms using rodent and primate models [1-5]. The authors focused on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, a functional molecule that exists in the postsynaptic membrane of synapses where neural information is transmitted, and developed a novel drug that promotes functional recovery after stroke. The development of a novel drug to promote functional recovery after stroke has been carried out and is reported here [6].

2. Current status and problems with neuroprotective and plasticity-inducing drugs

Neuroprotective and neuroplasticity-inducing drugs are two approaches to pharmacologically promote recovery of motor function after brain injury, and the current status of the development of these novel drugs is reviewed by Abe et al and Kumar et al [7,8].

2.1. Neuroprotective agents

The basic concept of neuroprotective drugs is to inhibit cell death by protecting neurons from overexcitation (excitotoxicity) and reactive oxygen species that occur after a stroke. The marketed drug Radicat (edaravone) has been shown to reduce the effects of free radicals. Other drugs in development include calcium channel inhibitors (nimodipine, flunarizine), N-methyl-D-aspartate receptor (NMDAR) inhibitors (MK-801), AMPA receptor inhibitors (ZK20075), γ-aminobutyric acid (GABA) receptor agonists (clomethiazole), and nitric oxide inhibitors [9]. 3K3A-activated protein C (3K3A-APC) is a protease-activated receptor 1 (PAR1) agonist with protective effects on neuronal and vascular endothelial cells and promotes vascular homeostasis. In the RHAPSODY trial, a phase II trial in stroke patients, it was found to reduce the volume of hemorrhage, but did not improve the modified Rankin Scale (mRS) score [10]. On the other hand, the development of NA-1/Tat-NR2B9c is also underway, and the point of action of NA-1 is the complex formation of NMDAR, post-synaptic density protein 95 (PSD-95), and neuronal nitric oxide synthase (nNOS) involved in the excitotoxic signaling cascade. Although there have been Phase II (ENACT [11]) and Phase III (ESCAPE-NA-1 [12]) trials in stroke patients, both showed a reduction in the number of cerebral infarctions, but no improvement in the motor function assessment system National Institutes of Health Stroke Scale (NIHSS) score and the mRS scores.

2.2. Neuroplasticity-inducing drugs

Neuroplasticity-inducing drugs include drugs that regulate neuroplasticity by adrenergic, dopaminergic, and serotonergic mechanisms, drugs that regulate axon elongation, and drugs that regulate the immune system.

Amphetamines are adrenergic agonists. Adrenergic agonists exert their sympathomimetic and centrally excitatory effects by inhibiting norepinephrine and dopamine reuptake and by increasing catecholamine levels at the synapse. Experiments with D-amphetamine in 1942 in cats, rodents, and other animals showed that it restored motor function in stroke models [7]. Subsequently, experiments in primates and various clinical trials in humans were conducted, but the results were inconsistent. A double-blind study was conducted, but the D-amphetamine group showed no effect on motor function recovery compared with the placebo group [13]. Amphetamine has also been used as an antihypertensive in the treatment of stroke in humans. Amphetamine is also a drug designated as a stimulant and has side effects, making its development in Japan difficult.

Dopamine agonists include L-DOPA, a typical drug for the treatment of Parkinson's disease. L-DOPA is a precursor of dopamine, and when it enters the brain from the bloodstream, it is converted to dopamine and shows medicinal effects. Although preclinical studies have shown that dopamine acts on the primary motor cortex and promotes neuroplasticity and motor learning, clinical trials in humans have shown inconsistent results [14,15].

Among serotonin agonists, selective serotonin reuptake inhibitors (SSRIs), widely known as antidepressants, have been reported to restore motor function in animal models and stroke patients [8]. A Phase II trial, the Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME) trial, was conducted and showed that fluoxetine (an SSRI) treatment promoted motor recovery after stroke [16]. Following the FLAME trial, a Phase III trial, the Fluoxetine

or Control Under Supervision (FOCUS) trial, was conducted, but no effect on motor function recovery was observed, as there was no change in the mRS score 6 months after stroke onset [17].

Drugs that control axon outgrowth are different from the aforementioned drugs in that they promote axon outgrowth and form new neuronal circuits, an approach that aims to restore motor function. Most of them have been reported as a therapeutic strategy for spinal cord injury models, but they have also been shown to restore axon elongation and motor function in stroke models [8]. The most advanced development is an antibody against myelin-associated glycoprotein (MAG), also known as anti-MAG (GSK249320), one of the inhibitors of axon elongation. Although it has been shown to restore motor function in rodent and primate models [18], no change in walking speed was observed in stroke patients treated with GSK249320 in a Phase IIb trial [19].

Maraviroc, a C-C chemokine receptor 5 (CCR5) inhibitor, was originally developed as a treatment for human immunodeficiency virus (HIV), but its application for the recovery of motor function after brain injury has been extended. It is expected to expand its application for the recovery of motor function after brain injury. There have been reports that suppression of CCR5 expression in a traumatic brain injury model resulted in the recovery of motor and cognitive functions and that human genetic analysis showed that stroke patients with CCR5 gene deletion (CCR5-Δ32) had good motor function [20,21]. A Phase II trial, the Maraviroc to Augment Rehabilitation Outcomes After Stroke (MAROS) trial, in stroke patients is currently underway, and the future of the trial is under scrutiny.

3. Synaptic migration of AMPA receptors.

Synapses are microstructures formed between neurons. When the presynaptic nerve induces an action potential in response to some stimulus, neurotransmitters (e.g. glutamate) are released from the presynaptic terminal, and the released neurotransmitters bind to receptors in the postsynaptic membrane of the postsynaptic nerve, where they form ion channels that allow ions to enter the cell and transmit information. The receptors, which form ion channels, allow ions to enter the cell, and information transmission takes place. AMPA receptors, NMDAR, and kainic acid receptors are among the postsynaptic receptors, and the authors focused on AMPA receptors, which play an important role in processes such as memory and learning. It has been suggested that “long-term potentiation (LTP)” is involved in the plastic changes that occur in the brain during learning and other processes [22]. The number of AMPA receptors in the postsynaptic membrane increases when synaptic transmission is enhanced in LTP [23,24]. Electrophysiological experiments using rat barrel cortex revealed that AMPA receptors migrate to synapses of neurons in the barrel cortex in dependence on sensory input from the whiskers (receptors for touch in rats [25]). In a study of motor learning in rats using rotor rods, a series of experiments, in which motor learning was impaired by the administration of an inhibitor of AMPA receptor function, also reported the synaptic transfer of AMPA receptors during motor learning [26]. Studies using rodent stroke models have suggested that AMPA receptors are involved in functional recovery after injury [27,28]. The authors further investigated the effects of AMPA receptors on motor learning and functional recovery after brain injury using a reaching task, a motor task in which mice grasp food with their forelimbs. When motor learning was performed in mice with AMPA receptor dysfunction (GluA1-c-tail) tagged with GFP (green fluorescent protein) in the unilateral primary motor cortex, the GFP-expressing group (control) showed an increased success rate in the reaching task, but not in the GFP-GluA1-c-tail-expressing group (Figure 1), indicating AMPA receptor synaptic transfer in the primary motor cortex is required for motor learning. Next, after 4 days of adequate learning of the reaching task, GFP-GluA1-c-tail or GFP was expressed in the

rostral periphery of the primary motor cortex; one week later, a mild freezing injury was produced in the unilateral primary motor cortex, and rehabilitation-like training was performed from the day after the injury for 3 weeks. The evaluation system calculated the relative recovery rate (performance score) by determining the percentage of success in grasping the food at a time (success rate), with "1" being the performance at the time of learning and "0" being the performance 21 days after injury. Improvement in the performance score was observed in the GFP-expressing group, but not the GFP-GluA1-c-tail-expressing group (Figure 1B and C). In other words, the recovery of motor function by rehabilitation after brain injury is dependent on the AMPA receptor synapse transfer [6].

4. Edonerpic maleate promotes AMPA receptor synaptic transfer

Edonerpic maleate, also known as T-817 maleate (1-{3-[2-(1-benzothiophen-5-yl)ethoxy]propyl} azetidin-3-ol;(*Z*)-but-2-enedoic acid), is a candidate compound for the treatment of Alzheimer's disease developed by Fujifilm Toyama Chemical Corporation and is known to have neuroprotective effects against oxidative stress and to promote neurite outgrowth (Figure 2A) [29]. The safety of the drug has been confirmed in healthy subjects and dementia patients [30,31]. The authors examined the ability of edonerpic maleate to transfer AMPA receptor synapses in the mouse somatosensory cortex by electrophysiological experiments. During development, AMPA receptor

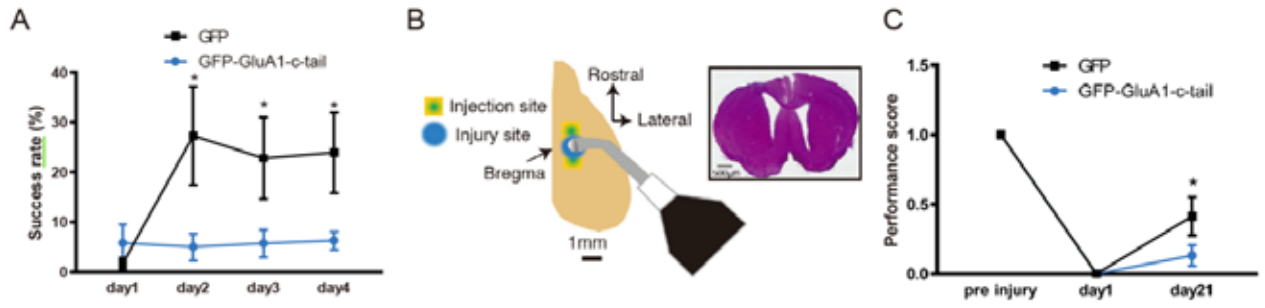

Figure 1. Synaptic AMPA receptor delivery-dependent acquisition of reaching task and functional recovery after mild cortical cryoinjury [6]. (A) Average success rates in the reaching task in mice injected with either GFP-tagged GluA1 c-tail or GFP-expressing lentivirus at layer 5 in the motor cortex forelimb area; (B, left) Schematic illustration of injection and injury site; (B, right) Representative of hematoxylin-eosin stained coronal sections including the mild cryoinjury. Scale bar, 500μm. (C) Average performance scores in the reaching task of mice injected with GFP-GluA1-c-tail or GFP expressing lentivirus using mice with mild cryoinjury.*$P < 0.05$. Data were analyzed with two-way ANOVA followed by Bonferroni's post hoc test.

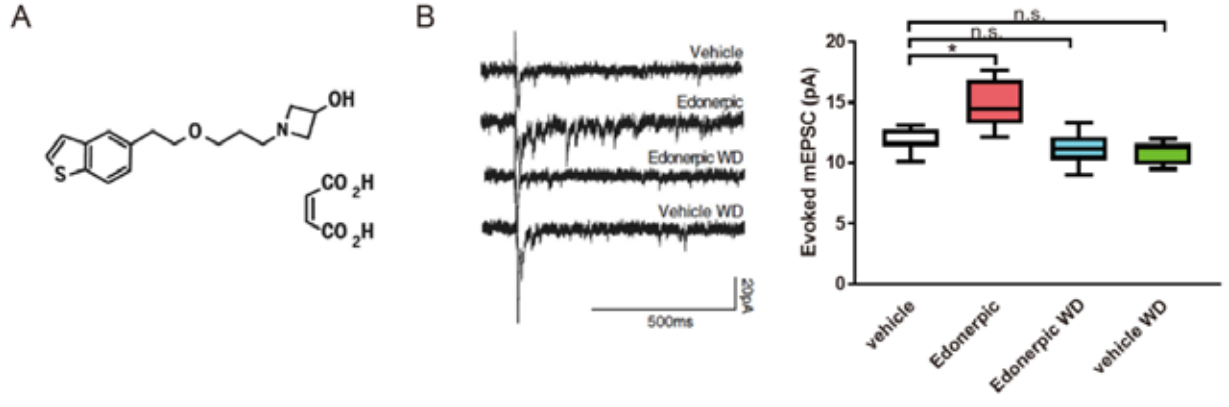

Figure 2. Edonerpic maleate promotes experience-dependent synaptic AMPA receptor delivery in mice barrel cortex [6]. (A) Chemical structure of edonerpic maleate; (B, left) Evoked mEPSC sweep; (B, right) Average amplitudes of evoked mEPSCs. WD: Whisker deprivation. *$P < 0.05$. Data were analyzed with one-way ANOVA, with Dunnett's post hoc test.

synaptic transfer at neuronal synapses in the somatosensory cortex does not occur in mice. After 3 weeks of oral administration of edonerpic maleate to these well-developed mice, in which AMPA receptor synaptic transfer does not occur, electrical activity was recorded from neurons in the somatosensory cortex, showing an increase in AMPA receptor-mediated currents (Figure 2B). However, when sensory input was cut off by severing the whiskers (tactile receptors) two days before the electrophysiological experiments, there was no increase in AMPA receptor-mediated currents (Figure 2B), indicating that AMPA receptor synaptic migration by edonerpic maleate is a sensory input-dependent phenomenon.

5. Effects of edonerpic maleate on promoting functional recovery after brain injury in rodent models

To test the medicinal effects of edonerpic maleate, a rodent model of frozen injury to the primary motor cortex was used. This is a model in which motor function does not recover spontaneously due to a severe brain injury (Figure 3A and B). After the mice had sufficiently learned the reaching task for 4 days, a freeze injury was created in the unilateral primary motor cortex, edonerpic maleate or water was orally administered for 8 weeks from the day after the injury, and rehabilitation-like training and motor function assessment using the reaching task were conducted for 5 weeks from 3 weeks after the injury. The performance score improved in the Edonerpic + training group as compared to the Vehicle + training group (Figure 3C). Surprisingly, no increase in the performance score was observed when edonerpic maleate was administered and no training was performed (Edonerpic + no training group, Figure 3C). In other words, in common with the results of the electrophysiological experiments described above, edonerpic maleate showed an activity-dependent recovery of motor function [6].

Next, brain regions involved in the medicinal effects of edonerpic maleate were explored. After confirming motor function recovery 28 days after injury in a system similar to the aforementioned experiment, a significant reduction in success rate was observed when the cortex around the rostral side of the injured area

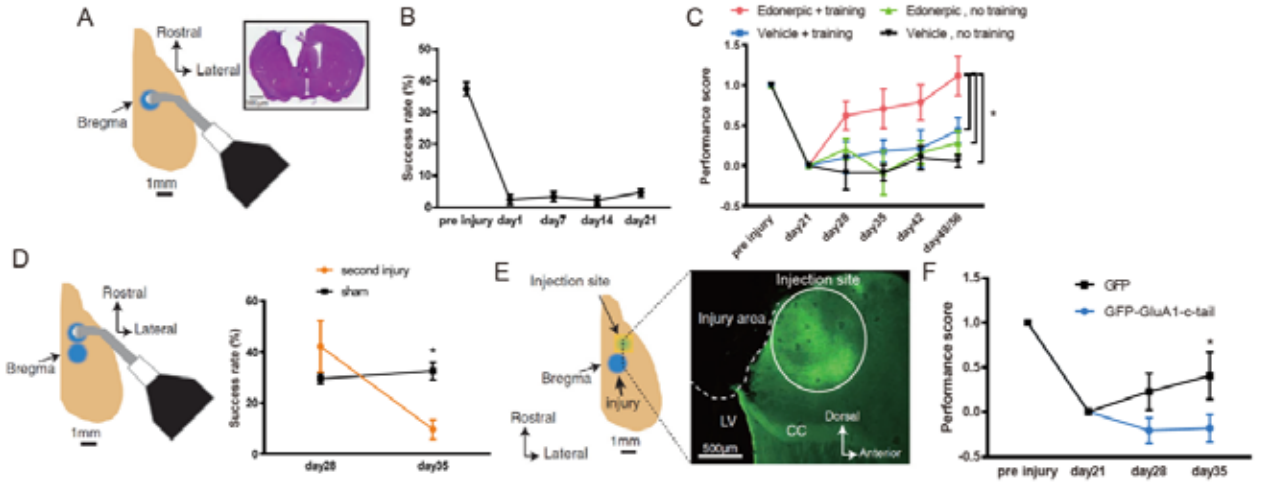

Figure 3. Edonerpic maleate facilitates motor function recovery in mice cryoinjury models [6]. (A, left) Schema of cryoinjury; (A, right) Hematoxylin-eosin-stained with severe cryoinjury; (B) Average success rate after cryoinjury; (C) Average performance score before and after injury; (D, left) Schematic diagram of the second lesion; (D, right) The average success rate on day 28 (before the second lesion) or 35 (after the second lesion); (E, left) Representative photomicrograph of the virus injection site; (E, right) GFP-expressing cells in the peri-injured cortex. The dotted line represents the cryo-injured region. The solid line represents the injected region. LV, lateral ventricle; CC, corpus callosum; (F) Average performance score in mice with GFP-GluA1-c-tail or GFP expression. *$P < 0.05$. Data were analyzed with two-way ANOVA, followed by Bonferroni's post hoc test in (A) and (D), and the unpaired *t*-test in (B).

was subjected to frozen brain injury (second injury) compared to the sham group (Figure 3D), indicating that the cortex around the injury plays a function in compensatory areas. In addition, electrophysiological experiments from neurons in the peri-injury cortex showed a significant increase in AMPA receptor-mediated currents in the Edonerpic group compared to the Vehicle group. Furthermore, when neurons in the peri-injury cortex expressed GFP-GluA1-c-tail or GFP alone before injury (Figure 3E), followed by edonerpic maleate administration and training, performance scores improved in the GFP-expressing group, but not in the GFP-GluA1-c-tail expression group (Figure 3F), indicating that synaptic migration of AMPA receptors in the compensatory cortex is necessary for motor function recovery. These results indicate that edonerpic maleate promotes AMPA receptor synaptic migration of neurons in the compensatory cortex around the injury and accelerates recovery of motor function in a rodent model of cortical freeze injury [6].

6. The medicinal effects of edonerpic maleate are mediated by collapsin-response-mediator-protein 2

The mechanisms underlying the medicinal effects of edonerpic maleate were explored. Using ligand phishing, it was found that edonerpic maleate binds to collapsing-response mediator-protein 2 (CRMP2). CRMP2 has been identified as an intracellular signaling protein for semaphorins, which were discovered as repulsive factors in nerve axons [32], and recently reported to be involved in synaptic function [33]. Next, to investigate the binding of CRMP2 to edonerpic maleate and the effect of AMPA receptors on synaptic migration, electrophysiological experiments were performed using CRMP2 knockout (KO) mice. When AMPA receptor-mediated currents were measured in adult wild-type (WT) and CRMP2 KO mice after 3 weeks of treatment with water or edonerpic maleate, no changes in currents due to edonerpic maleate were observed in CRMP2 KO mice (Figure 4A), indicating that the currents were not altered by edonerpic maleate in these mice. The enhancement of AMPA receptor synaptic migration observed in edonerpic maleate was mediated by CRMP2. To further investigate whether CRMP2 signaling is involved in the recovery of motor function, behavioral experiments were conducted using CRMP2 KO mice. After learning a reaching task, the unilateral primary motor cortex was cryoinjured, and edonerpic maleate or water was administered for 8 weeks from the day after the injury, followed by training and motor function assessment 3 weeks after injury. However, in CRMP2 KO mice,

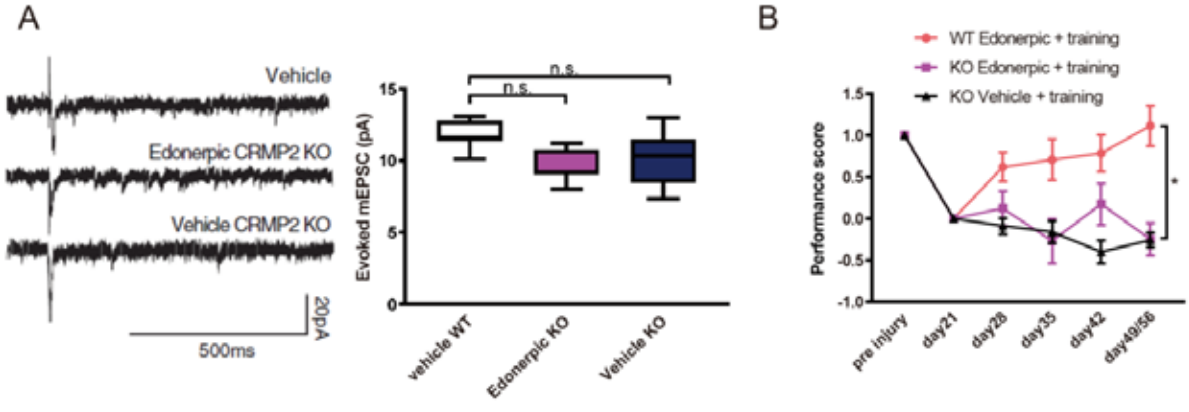

Figure 4. CRMP2 mediates edonerpic maleate-induced functional recovery [6]. (A, left) Evoked mEPSC in the barrel cortex in CRMP2 knockout mice; (A, right) Average amplitudes of evoked mEPSCs; (B) Average performance score. WT mice data were derived from **Figure 3A**. CRMP2 knockout data were added. *$P < 0.05$. Data were analyzed with one-way ANOVA, with Dunnett's post hoc test in (A), and Bonferroni's post hoc test in (B).

the performance score was not improved by edonerpic maleate administration (**Figure 4B**). These results indicate that edonerpic maleate has a medicinal effect in promoting synaptic migration of AMPA receptors by using CRMP2 as a target molecule and also in restoring motor function [6].

7. Edonerpic maleate promotes functional recovery after brain injury in primate models

As it is essential to study the effects of edonerpic maleate in higher animals for drug development, the drug efficacy of edonerpic maleate was evaluated in primates, which have fine motor skills in their upper limbs. Adult crab-eating macaques were used as experimental animals, and after 20 days of adequate learning of the reaching task (simple reach-to-grasp task) and the vertical slit task, collagenase IV was injected locally into the unilateral entrapment under MRI guidance to create a model of entrapment hemorrhage. After the injury, the use of the paralyzed limb was confirmed in each task, followed by the administration of edonerpic maleate or solvent (vehicle) intramuscularly, rehabilitation-like training, and motor function assessment were performed for approximately 2 months. In the simple reach-to-grasp task (Figure 5A), the time required from reaching to grasping the food was assessed, and in the vertical slit task (Figure 5B), the success rate of grasping the food without dropping it and the time required to grasp the food were measured, and the relative recovery rate (performance score) was calculated, with the performance at the time of learning as "1" and the performance at the first assessment after injury as "0". In the simple reach-to-grasp task, the edonerpic maleate group showed an improvement in the performance score from early treatment and maintained it until the last stage of treatment (Figure 5C). In the vertical slit task, the edonerpic maleate group also showed an improvement in the performance score from the early stage of treatment and was maintained until the last stage of treatment (Figure 5D). Furthermore, the edonerpic maleate group showed a higher performance score in the time required to grasp the food in the late administration phase. These results indicate that edonerpic maleate has a restorative effect on locomotor function in the higher primate model of entrapment hemorrhage [6].

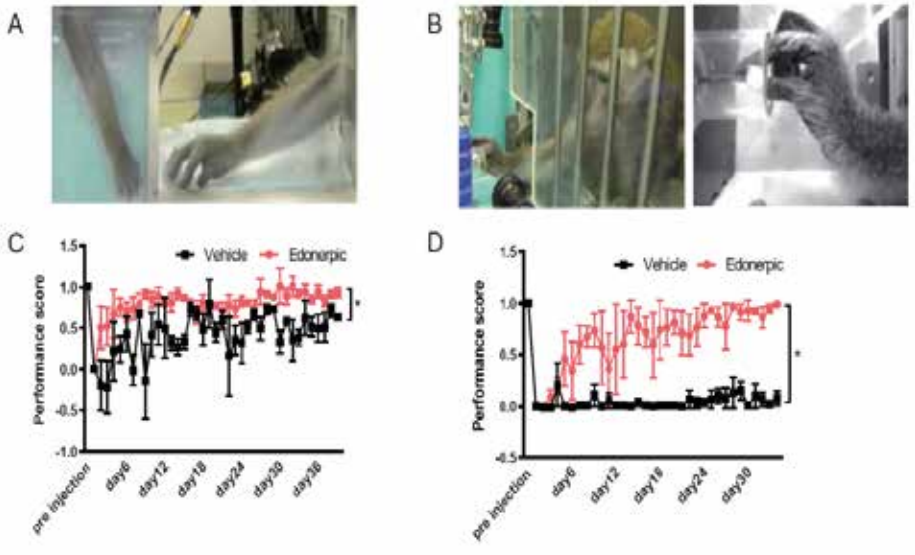

Figure 5. Edonerpic maleate accelerates motor function recovery in primates [6]. (A) Simple reach-to-grasp task; (B, left) Vertical slit task; (B, right) The finger-thumb grip in the vertical slit task before the injury; (C) Time course of the performance score in the simple reach-to-grasp task; (D) Time course of the performance score for successful retrievals in the vertical slit task. *$P < 0.05$. Data were analyzed with two-way ANOVA in (C) and (D).

8. Conclusion

Various neuroplasticity-inducing drugs have been developed so far, with promising results in the preclinical studies, but have failed in the clinical trials in humans. This may be due to the neural circuits of the whole brain being activated in a disorderly manner and the neural circuits necessary for rehabilitation are not selectively activated. Edonerpic maleate was found to selectively activate the neural circuits relevant to rehabilitation, and promote recovery of motor function without side effects. A Phase II clinical trial is currently underway in stroke patients, and future prospects are promising (jRCT2031190110).

Disclosure statement

The authors declare no conflict of interest.

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