学位論文の要旨

CRMP2-binding compound, edonerpic maleate accelerates motor function recovery from brain injury

(CRMP2 に結合する低分子化合物 edonerpic maleate の脳損傷後運動機能回復促進作用)

Hiroki Abe

Physiology

Yokohama City University Graduate School of Medicine

Doctoral Supervisor：Takuya Takahashi, Professor

Summary

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http://science.sciencemag.org/content/360/6384/50/tab-pdf

Background

Pharmacological intervention to enhance rehabilitation from stroke have been investigated in animal models and clinical trials with focuses on neuro modulatory pathways. While certain small-scale studies have suggested that dextroamphetamine, L-3,4-dihydroxyphenylalanine, and selective serotonin uptake inhibitors enhance motor function recovery, larger studies such as randomized controlled trials have failed to reveal a promoting effect. Thus, the concept of pharmacological enhancement for stroke rehabilitation needs to be reconsidered. Here, we propose a concept that it could be a rehabilitation-accelerating strategy to modulate the glutamate receptors trafficking to post synaptic membrane in non-injured lesions after brain damage.

Materials and Methods / Results

Based on the concept described above, we aimed to develop a rehabilitation accelerating agent to facilitate AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic-acid) receptors trafficking to the post synaptic membrane. To identify a small compound which could enhance AMPA receptors trafficking, we focused on layer 4/2-3 pyramidal synapses in the mice barrel cortex (a sensory cortex responsible for sensory inputs from whiskers), where the sensory experience - dependent AMPA receptor trafficking occurs in the neonate but not in the adult. After administering each compound, electrophysiological response was evaluated in synapses within the layers 4/2-3 of the adult mice barrel cortex. Using this screening strategy in vivo, we found that edonerpic maleate has the potential to enhance AMPA receptors trafficking even in the adult mice barrel cortex. Interestingly, we also found that edonerpic maleate facilitates synaptic AMPA receptor trafficking only in the presence of whiskers. Then, we tried to identify the target molecule of edonerpic maleate using mass spectroscopy and found that it binds to collapsin response mediator protein 2 (CRMP2). We also found that edonerpic maleate -CRMP2 complex activates actin depolarizing factor (ADF)/cofilin in a plasticity inducing condition.

The effect of edonerpic maleate on the motor function recovery was first examined in rodents. After the mice successfully learned the reaching forelimb task, we introduced a cryoinjury in their motor cortex. For at least 3 weeks, these mice persistently failed in the performance of reaching task that evaluates forelimb reaching. We examined the efficacy of edonerpic maleate in these mice. Mice administered with edonerpic maleate (30 mg/kg, twice a day) during rehabilitative training for 3 weeks following the introduction of cryoinjury showed a marked recovery compared to control mice. Interestingly, mice administered with edonerpic maleate (30 mg/kg, twice a day) without rehabilitative

training showed no recovery. These results suggested that edonerpic maleate promotes motor function recovery after brain damage in a training - dependent manner. We also confirmed the same efficacy of the compound at the dose which was proven to be safe in human clinical trial. We next evaluated the effect of edonerpic maleate in non-human primate model. To evaluate the efficacy of edonerpic maleate in non-human primates, we introduced an internal capsule hemorrhage (ICH) by a focal stereotaxic injection of collagenase. Following this induction, the animal showed severe disabilities in forelimb reaching and manual dexterity. Subsequently, we evaluated the forelimb function and manual dexterity in non-human primates treated with edonerpic maleate in combination with rehabilitation. We observed the robust effect of edonerpic maleate on motor function recovery after ICH. We therefore demonstrated remarkable effects of edonerpic maleate on motor function recovery not only in rodents but also in non-human primates.

Discussion

The efficacy of edonerpic maleate in stroke should be tested in clinical trials at the earliest. To further screen a more effective compound, pharmacological and biological mechanism of edonerpic maleate such as signaling pathway to facilitate synaptic AMPA receptor delivery should be studied. Recently, the constrained induced therapy, robotics, and repetitive transcranial magnetic stimulation has been introduced at the clinical site. Thus, combinatorial approaches of these technologies with pharmacological intervention with edonerpic maleate could maximize the potential of our medical options for the treatment of brain damage such as stroke.

Keywords

Rehabilitation, AMPA receptors, CRMP2, Edonerpic maleate

Reference

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Publication list

Main article

CRMP2-binding compound, edonerpic maleate, accelerates motor function recovery from brain damage

Hiroki Abe*, Susumu Jitsuki*, WakiNakajima*, Yumi Murata*,Aoi Jitsuki-Takahashi, Yuki Katsuno, Hirobumi Tada, Akane Sano, Kumiko Suyama, Nobuyuki Mochizuki, Takashi Komori, Hitoshi Masuyama, Tomohiro Okuda, Yoshio Goshima, Noriyuki Higo, Takuya Takahashi

(* equal-contribution)

Science, Vol.360, page 50-57, 2018

Sub article

None

Reference article

None