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Research paper

Constraint-induced movement therapy improves efficacy of task-specific training after severe cortical stroke depending on the ipsilesional corticospinal projections

Naohiko Okabe[a,*], Naoyuki Himi[a], Emi Nakamura-Maruyama[a], Norito Hayashi[a,b], Issei Sakamoto[a,b], Kazuhiko Narita[a], Toru Hasegawa[b], Osamu Miyamoto[a]

[a] Second Department of Physiology, Kawasaki Medical School, 577, Matsushima, Kurashiki City, Okayama 701-0192, Japan
[b] Department of Orthopedic Surgery, Kawasaki Medical School, 577, Matsushima, Kurashiki City, Okayama 701-0192, Japan

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ABSTRACT

Descending spinal pathways (corticospinal, rubrospinal, and reticulospinal) are believed to contribute to functional recovery resulting from rehabilitative training after stroke. However, the contribution of each pathway remains unclear. In the current study, we investigated rehabilitation-induced functional recovery and remodelling of the descending spinal pathways after severe cortical stroke in rats followed by 3 weeks of various rehabilitation [constraint-induced movement therapy (CIMT), skilled forelimb reaching, rotarod, and treadmill exercise]. Following photothrombotic stroke, 96% of corticospinal neurons in the ipsilesional motor cortex were destroyed. Despite the preservation of 82% of total spinal projection neurons (e.g. rubrospinal and reticulospinal projection neurons), rats showed persistent and severe disability, especially in skilled motor function. In this severe stroke model, only CIMT promoted functional recovery, associated with increased corticospinal projections from the peri-infarct motor cortex. Rehabilitation-induced recovery was reversed when the restored corticospinal neurons were destroyed by a second stroke. These data indicate that training-induced functional recovery is dependent on ipsilesional corticospinal projections, which highlights the importance of using strategies to enhance survival, axonal remodelling, or regeneration of corticospinal neurons to effectively restore function in severely affected stroke patients.

1. Introduction

Upper limb disability is a common problem in post-stroke patients, and task-specific training is regarded as the most reliable therapy (Winstein et al., 2016). Although rehabilitative training promotes functional recovery in a task-specific manner, the efficacy of training strongly depends on the severity of brain damage. Specifically, functional outcome in chronic stroke patients depends on the integrity of the corticospinal tract (Stinear et al., 2007). Similarly, while skilled forelimb training effectively recovers precise forelimb movement after destruction of the primary motor cortex (caudal forelimb area; CFA) in rats, rehabilitative training cannot achieve measurable recovery when both the primary and secondary motor cortex (rostral forelimb area; RFA) are destroyed (Okabe et al., 2016). We previously demonstrated that task-specific training promotes axonal remodelling in the corticospinal pathway originating from the ipsilesional cerebral cortex only, and not the contralesional corticospinal pathway nor the descending spinal pathways from deep brain areas (e.g. rubrospinal and reticulospinal pathways) (Okabe et al., 2017). This suggests that limited axonal remodelling may restrict the recovery induced by task-specific training after severe stroke.

In preclinical stroke research, several innovative therapies have been proven to amplify functional recovery during rehabilitative training through enhancement of axonal remodelling. These include anti-NogoA immunotherapy (Wahl et al., 2014), chondroitinase ABC therapy (Wiersma et al., 2014), and optogenetic brain stimulation (Wahl et al., 2017). However, none of these have translated to the clinic. Therefore, optimization of rehabilitative training should be a leading strategy to maximize post-stroke recovery. In the clinical setting, various training methods are currently used for post-stroke rehabilitation (e.g. aerobic training, balance training, and task specific training, Dobkin and Dorsch, 2013); however, the effects of these training paradigms on axonal remodelling is unclear. Because axonal remodelling after brain injury is activity-dependent (Carmel and Martin, 2014), and different motor tasks induce distinct patterns of regional brain activation (MacLellan et al., 2011), it is likely that

* Corresponding author.
E-mail address: n-okabe@med.kawasaki-m.ac.jp (N. Okabe).

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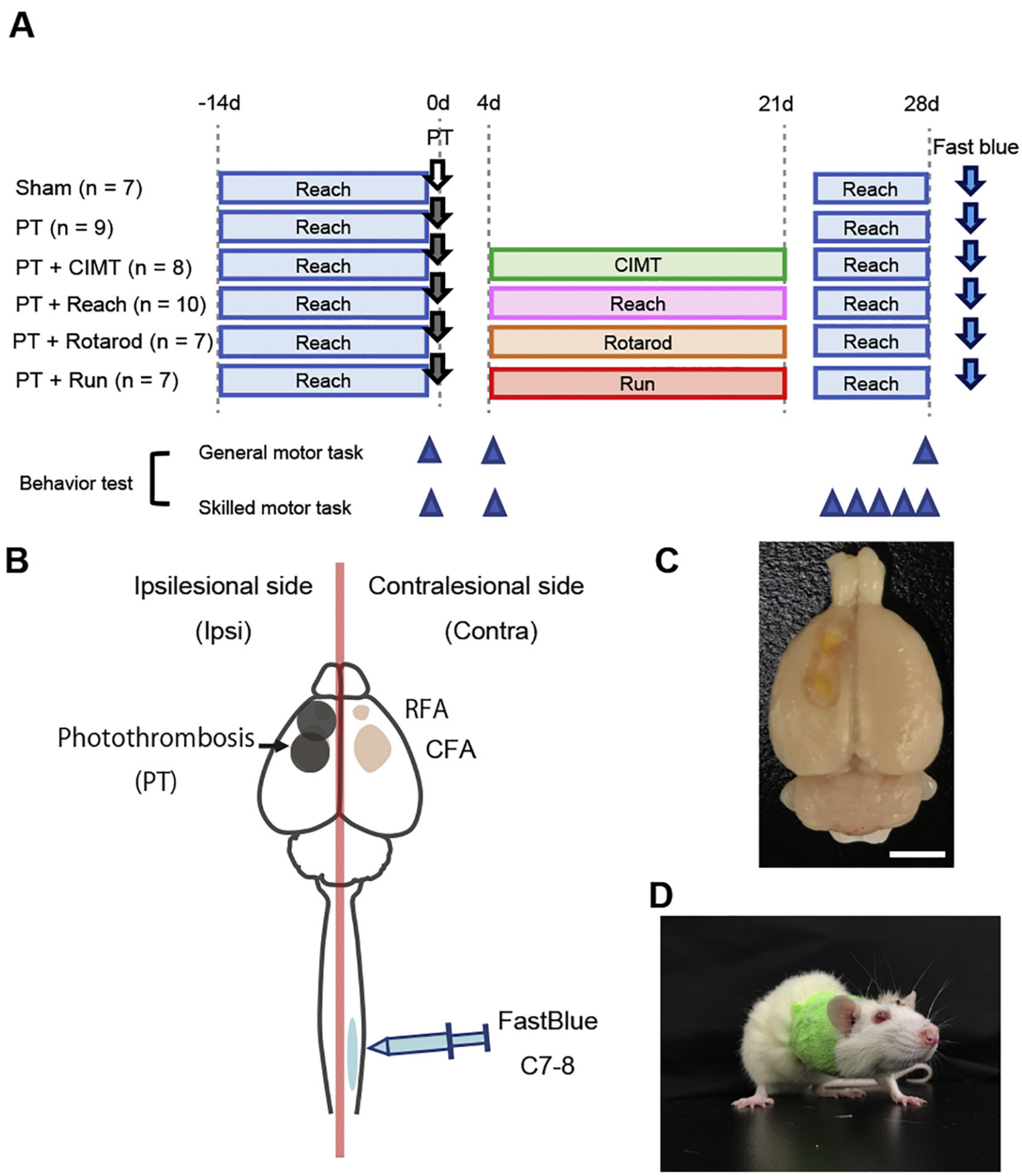

Fig. 1. Experimental design. (A) Experimental groups and schedule. (B) Fast blue injection. Orange areas indicate forelimb area (divided into RFA and CFA). Black circles indicate infarct induced by PT. (C) Representative image of a brain following PT. Scale bar = 5 mm. (D) Representative picture of a rat receiving CIMT. CFA, caudal forelimb area; CIMT, constraint-induced movement therapy; PT, photothrombotic stroke; RFA, rostral forelimb area.

different types of training cause axonal remodelling in different parts of the neural network and with varying efficiency. Furthermore, the effects of rehabilitative training are affected by any combined therapy, as well as the timing of training (Wahl and Schwab, 2014). Therefore, understanding how various types of training distinctively modulate neural network remodelling, and how they interact with each other, is essential to optimize combinatorial rehabilitative schedules.

In this study, we assessed whether acute rehabilitative training affects functional recovery induced by multiple types of trainings (Fig. 1A) following severe photothrombotic (PT) stroke in the rat (Fig. 1B and C). Training paradigms included constraint-induced movement training (CIMT; Fig. 1D), skilled forelimb training (Reach), Rotarod training, and treadmill exercise (Run). All of these strategies have been reported to significantly improve functional recovery after stroke (Mosberger et al., 2017; Himi et al., 2016; Ishida et al., 2016; Nakagawa et al., 2013; Schmidt et al., 2014), and require different types of physical activity: CIMT involves constraint-induced use of the affected limb during daily tasks, Reach requires precise skilled movements with the affected limb, Rotarod involves coordinated balance, and Run involves aerobic exercise. We then assessed how these training paradigms affect neural network remodelling following stroke using retrograde tracing of descending spinal projections (Fig. 1B). Our findings demonstrate that rehabilitation-induced functional recovery is severely impeded when the majority of ipsilesional corticospinal neurons are destroyed, regardless of the training method applied, and that restoration of corticospinal neurons is fundamental for rehabilitation-induced task-specific recovery.

2. Material and methods

2.1. Animals

We used a total of 68 adult male Fisher 344 rats (9 weeks old at the beginning of training; 160–180 g; Charles River Laboratories Japan,