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Review article

Reorganization of motor circuits after neonatal hemidecortication

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ABSTRACT

It is well recognized that a juvenile brain is more plastic than an adult brain and often undergoes better functional recovery following cortical injury. Infants treated with hemispherectomy to cure intractable epilepsy often exhibit restored normal motor function in the extremities contralateral to the lesion. Neuronal mechanisms of functional recovery after such a large cortical damage at a young age have been studied using animals with a similar lesion, hemidecortication. In such animals, descending pathways from the undamaged sensorimotor cortex to the ipsilateral forelimb motoneurons are reorganized as restoring normal motor function of the forelimb contralateral to the injury. Similar aberrant pathways from the motor cortex to the ipsilateral motoneurons are also generated following suppression of cortical activity in the other hemisphere, suggesting the development of contralateral connections in an activity-dependent manner in normal animals. Thus, formation of ipsilateral descending pathways following neonatal hemidecortication might be due to a loss of balance in cortical activity between the two hemispheres. Studies using animal models of neonatal cortical injury can reveal mechanisms of neural development and may help to establish therapeutic strategies to facilitate recovery from human juvenile cortical injury.

Contents

1. Introduction

A juvenile brain is more plastic than an adult brain and often undergoes more rapid recovery of sensory motor function and exhibits less severe deficits following injury. Cerebral hemispherectomy, a procedure in which a cortical hemisphere with abnormal development is surgically removed, has been performed in children who have intractable seizures. One major consequence of comparable brain injury in adulthood is complete hemiparesis or loss of sensation on the side opposite to the injury. However, the same operation in the young rarely results in a complete loss of motor function and sensation (Wilson, 1970; Peacock et al., 1996; Mathern et al., 1999; Devlin et al., 2003; van Empelen et al., 2004). In cases of hemispherectomy in the young, a negative correlation exists between the extent of motor recovery and age at the time of the surgery (Choi et al., 2010). Age-related recovery after the large cortical lesion is often seen in clinical cases.

Here, we review reports of animal experiments on neuronal mechanisms underlying motor recovery following early cortical injury. In particular, we focus on the juvenile hemidecortication

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model, in which one cortical hemisphere is completely or semi-completely removed or inactivated at the neonatal stage. The experimental model not only clarifies neuronal mechanisms underlying behavioral recovery from early cortical injury, but may also open new perspectives on the plasticity of corticospinal circuitry. For information on other experimental models of motor deficits, such as injury of the whole cortex (decortication) or focal lesions to specific cortical areas, we refer readers to other references of these models (Kolb and Whishaw, 1989; Kolb et al., 2000; Kolb and Gibb, 2007).

2. Animal model of young cortical injury

The great potential for behavioral recovery of a juvenile brain after damage has been recognized for over 100 years. In the late 1930s and early 1940s, Margaret Kennard and her colleagues experimentally confirmed this notion using monkeys (Kennard, 1936, 1938, 1942). In a series of their experiments, lesions of the motor cortex in developing monkeys resulted in less sever motor deficits than those in adults, which suffered from paresis after comparable lesions. This idea was so influential that the concept was subsequently referred to as the 'Kennard principle' by Hans-Lukas Teuber (1974). Today, the notion has percolated through neuroscience communities and the general public.

About 30 years after the Kennard reports on the superior plasticity of juvenile brains following cortical damage, researchers re-started studies on the restoration of sensory motor function after juvenile cortical injury using an animal model with neonatal hemidecortication. Hicks and D'Amato (1970, 1975) first showed that rats that suffered from hemidecortication at birth showed movement responses to lateral tactile stimuli to the forelimb contralateral to the hemidecortication (i.e., the affected forelimb) similar to those of normal rats before post-natal day (PND) 17. On the other hand, rats that received a cortical lesion in adulthood did not exhibit such functional restoration following the injury. As these lesions were extended to subcortical regions in later studies, the extent of the behavioral restoration was much lower than that of the purely hemidecorticated animals even in the young, although there was a clear age-effect (Kolb and Tomie, 1988; Whishaw and Kolb, 1988; Takahashi et al., 2009). Even though forelimb movements were elicited reflexively in the lateral tactile test, these studies indicated that animals with juvenile hemidecortication are a good model to investigate brain plasticity after damage to the nervous system. Neonatally lesioned animals could also show stimulus-induced behaviors, including sensory responses to a tactile stimulation presented to the body contralateral to the cortical lesion and withdrawal responses of the affected forelimb from water at innoxious or noxious temperatures (Schallert and Whishaw, 1984, 1985; Burgess and Villablanca, 1986; Villablanca et al., 1986; van Hof et al., 1987; Armand and Kably, 1993; Burke et al., 2012). Functional sparing of the affected forelimb of hemidecorticated animals was later assessed using behavioral performance of skilled movements (Burgess and Villablanca, 1986; Kolb and Tomie, 1988; Whishaw and Kolb, 1988; Takahashi et al., 2009), which are generated internally and controlled by motor commands from the motor cortex via the corticofugal pathways. Thus, when juveniles undergo cortical lesions, the sensory motor functions of their affected forelimbs, including both reflexes and voluntary movements, are spared.

Which brain regions contribute to the sparing of motor function in the affected forelimbs of juvenilely hemidecorticated animals? After neonatal hemidecortication in rats, the remaining intact cortex contralateral to the lesion became thicker relative to the same hemisphere of normal controls (Kolb et al., 1983; Kolb and Tomie, 1988; Kolb et al., 1992). Involvement of the intact cortex in behavioral restoration after juvenile cortical lesion was examined by making a second lesion in the intact sensorimotor cortex in adult rats (Barth and Stanfield, 1990; Takahashi et al., 2009). Following these second lesions, the rats could not move the originally affected forelimb as well as the intact forelimb (contralateral to the second lesion) in both a lateral tactile placing task and a reach to grasp task. On the other hand, a second lesion to the intact cortex of rats that received a first cortical lesion in adulthood did not decrease task performance of the affected forelimb. Thus, neuronal mechanisms of functional sparing following juvenile hemidecortication were different from those following hemidecortication in adulthood. In rats with neonatal hemidecortication, activation of the intact hemisphere by intracortical electrical microstimulation induced low-threshold movements in the ipsilateral affected forelimb (Kartje-Tillotson et al., 1985; Kartje-Tillotson et al., 1987). The same stimulation protocol never elicited movements of the affected forelimb after medullary pyramidotomy. Thus, lost function to control the contralesional forelimb movements was compensated for by the intact cortex in neonatally hemidecorticated rats.

3. Reorganization of cortical descending pathways in neonatally hemidecorticated animals

Involvement of the intact cortex in the compensation of the contralesional forelimb movements suggests that corticofugal pathways have some roles in the skilled movements in juvenilely hemidecorticated rats. What neural substrates underlie the functional sparing of the affected forelimb in hemidecorticated animals? In parallel with behavioral assessments of juvenilely hemidecorticated rats, Hicks and D'Amato (1970) used the Fink-Heimer–Nauta method to trace the trajectories of corticofugal fibers to examine the correlation between anatomical and behavioral changes in rats whose frontal cortex was damaged at birth or in adulthood. Neonatally hemidecorticated rats had sparse, uncrossed corticospinal fibers in the medulla and spinal cord, while there was no evidence of such an uncrossed tract in rats with adult hemidecortication. Further experiments using various neural tracing methods and electron microscopic observation of horseradish peroxidase-labeled fibers confirmed that the number of ipsilateral descending fibers originating from the intact cortex substantially increased in juvenilely hemidecorticated rats (Fig. 1) (Leong and Lund, 1973; Leong, 1976; Barth and Stanfield, 1990; Ono et al., 1990; Ono et al., 1991; Ono et al., 1994). Precise observation of corticospinal fibers labeled with anterograde tracers clarified that aberrant fibers in the ipsilateral spinal cord were acquired not by uncrossing at the pyramidal decussation but by re-crossing the midline from the contralateral dorsal funiculus at the local spinal segments (Fig. 2A) (Kuang and Kalil, 1990; Rouiller et al., 1991; Takahashi et al., 2009). Ipsilateral corticospinal projections from the intact cortex were also observed in juvenilely hemidecorticated cats and hamsters (Gomez-Pinilla et al., 1986; Kuang and Kalil, 1990).

Reorganization of the corticofugal fibers was detected not only in the spinal cord but also in other motor-related relay regions (Fig. 1). Ipsilateral projections to the pontine nuclei are important for cerebro-cerebellar interaction and smooth control of movements (Allen and Tsukahara, 1974; Nagao, 2004). In addition to the ipsilateral corticopontine projection, the contralateral pontine nuclei received crossed corticopontine fibers arising from the intact cortex in hemidecorticated rats (Leong and Lund, 1973; Castro, 1975; Leong, 1976; Kartje-Tillotson et al., 1986). The distribution of the contralateral corticopontine fibers was topographically similar to normal ipsilateral projections (Kartje-Tillotson et al., 1986). Ipsilateral projections to the red nucleus are required for interplay with outputs from the cerebellum (Toyama et al., 1970; Allen