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Research report

role of IGF-1 in cortical plasticity and functional deficit induced by sensorimotor restriction

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HIGHLIGHTS

- Sensorimotor restriction affects cortical organization and paw withdrawal.
- IGF-1 prevents cortical shrinkage, and partially receptive field enlargement.
- IGF-1 does not prevent the changes in sensibility threshold.
- IGF-1 prevents alteration of the paw withdrawal score.

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ABSTRACT

In the adult rat, sensorimotor restriction by hindlimb unloading (HU) is known to induce impairments in motor behavior as well as a disorganization of somatosensory cortex (shrinkage of the cortical representation of the hindpaw, enlargement of the cutaneous receptive fields, decreased cutaneous sensibility threshold). Recently, our team has demonstrated that IGF-1 level was decreased in the somatosensory cortex of rats submitted to a 14-day period of HU. To determine whether IGF-1 is involved in these plastic mechanisms, a chronic cortical infusion of this substance was performed by means of osmotic minipump. When administered in control rats, IGF-1 affects the size of receptive fields and the cutaneous threshold, but has no effect on the somatotopic map. In addition, when injected during the whole HU period, IGF-1 is interestingly implied in cortical changes due to hypoactivity: the shrinkage of somatotopic representation of hindlimb is prevented, whereas the enlargement of receptive fields is reduced. IGF-1 has no effect on the increase in neuronal response to peripheral stimulation. We also explored the functional consequences of IGF-1 level restoration on tactile sensory discrimination. In HU rats, the percentage of paw withdrawal after a light tactile stimulation was decreased, whereas it was similar to control level in HU-IGF-1 rats. Taken together, the data clearly indicate that IGF-1 plays a key-role in cortical plastic mechanisms and in behavioral alterations induced by a decrease in sensorimotor activity.

1. Introduction

Prolonged bed-rest, ageing, or even extreme conditions such as spaceflight, are characterized by a chronic reduction in neuromuscular activity. In humans, these situations result in a profound alteration in motor task performance (posture, gait, functional mobility...) (for review [22,38,44]). These impairments are due to a combination of factors including muscle alteration and plastic changes in neural function throughout the nervous system [8].

Hindlimb unloading (HU) is a rodent model of disuse commonly used to improve our understanding on effects of confinement to bed or sensorimotor restriction [31]. During HU, the contact of the plantar sole of the hindlimb with the ground is prevented and the proprioceptive input from the limb is dramatically reduced. This elevation of the lower limbs during 14 days induces impairments in the postural and locomotor tasks [4], which might be the result of an alteration in the functioning of supraspinal structures. Through cortico-cortical loops linking sensory and motor cortices, an alteration of the somatosensory pathway in HU rats might impact the cortical control of muscles. As a matter of fact, our previous

Abbreviations: HU, hindlimb unloading; RF, receptive field; C, control; IGF-1, insulin-like growth factor-1.

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studies have shown that HU has deleterious effects on the functioning of somatosensory cortex. A shrinkage of the foot somatotopic representation and an enlargement of the cutaneous receptive fields (RFs) [15,26] are reported. In addition, cortical neurons are activated for lower pressure applied on the paw, i.e. tactile sensitivity is increased. However, the mechanisms involved in these plastic mechanisms are still unclear, even if implication of neurotransmitters [6,10], or neurotrophins [17], and their associated signaling pathways [18] have been shown. In particular, we have recently shown that the decrease in sensorimotor activity in HU rats is accompanied by a decrease in IGF-1 (insulin-like growth factor 1) level in the somatosensory cortex [32].

Present in many tissues, IGF-1 is a growth factor playing a key-role in the brain. Although it may be produced within the brain, the major part of its cerebral effects is due to IGF-1 produced by the liver and transported by the blood stream. Its entrance into the brain is activity-dependent since serum IGF-1 crosses the blood-brain-barrier specifically in activated brain areas [34]. Several publications suggest that IGF-1 might mediate the beneficial effects of exercise on the brain [7,13,28]. Indeed, IGF-1 level is increased during exercise ([41]; see however [23]); IGF-1 modulates neuronal excitability [35] and dendritic growth [33]; it also affects the extent of cutaneous RFs in the dorsal column nuclei [35].

Given the adverse effects of HU on the somatosensory cortex organization, and the beneficial effects of IGF-1 on cortical plasticity, our hypothesis is that the decrease in IGF-1 observed in HU rats participates to the disorganization of the somatosensory cortex during HU. Thus, the question that arises is whether a restoration of the IGF-1 level in the somatosensory cortex could prevent the alteration induced by HU. Therefore, the first objective of the present study was to determine the effects of an IGF-1 infusion on the somatosensory cortex during the whole unloading period, by evaluating the size of the hindlimb representation in somatosensory cortex, the extent of receptive fields and the cutaneous sensibility threshold. The second objective was to evaluate the functional consequences of IGF-1 level restoration on tactile sensory discrimination.

2. Materials and methods

2.1. Ethics statement

All procedures described below were carried out in accordance with the European Communities Council Directive 2010/63/UE, and were approved by the Regional Committee on the Ethics of Animal Experiments of the Nord-Pas-de-Calais region (CEEA 75, reference Number: 02472.01). All efforts were made to minimize the number of animals and their suffering.

2.2. Animals

Male Wistar rats (280–320 g) were housed under temperature and light controlled conditions (23 °C, 12-h light/12-h dark cycle). Rats were acclimated at least one week after their arrival to the animal facility. They had ad libitum access to food and water and were regularly handled. Body weight was monitored 3 days/week.

2.3. Hindlimb unloading model

Hindlimb unloading was performed using the tail suspension model [31]. The tail was surrounded with a hypoallergenic adhesive tape (Elastoplast) and connected to a bracket, provided with a rotation of 360°. The height was adjusted to obtain a 30° inclination angle of the rat body with the horizontal. HU prevents the contact of the hindlimbs with the ground, whereas the rats are allowed to walk freely on their forelimbs. Control (C) and HU rats were housed in the same room. HU rats could have social interactions with their neighbors, and C animals were housed 3 per cage.

2.4. Chronic infusions of IGF-1

Two groups of rats (IGF-1 and HU-IGF-1) received a chronic infusion of IGF-1 (human IGF-1, 50 μg/mL; Peprotech) on the cerebral cortex. The infusion was achieved via a cannula attached with a flexible catheter to an osmotic minipump (200 μL reservoir, model 2002, Alzet), which ensures constant delivery of the substance for 2 weeks at the normal pumping rate of 0.48 μL/h. Pumps and catheters were primed by soaking in saline overnight. Implantation of the osmotic minipump was performed under strict aseptic conditions. The rats were anesthetized (ketamine 100 mg/kg, xylazine 20 mg/kg and acepromazine 3 mg/kg, i.p., Ceva Animal Health). Body temperature was maintained around 37 °C with a heating pad. Lidocaine was applied on ear bars and the head was placed in a stereotaxic frame. A burr hole was performed on the right side of the skull at the point of cannula insertion (3.5 mm posterior to Bregma, 3 mm lateral), at a point estimated to be just posterior to the hindlimb cortical representation area. The cannula tip was not in contact with the brain, and was fixed on the skull with 3 screws and acrylic cement (TAB 2000, Kerr). The pump was placed subcutaneously on the back of the rat. The incision was closed with silk suture and antiseptic (Betadine®) was applied on incision zones. Rats were kept on a heating pad in a cage until they recovered consciousness. Some rats were sham-operated (C-Sham and HU-Sham) and received only vehicle (artificial cerebrospinal fluid composed of NaCl 117 mM; KCl 4.7 mM; $CaCl_2$ 2.5 mM; $MgCl_2$ 1.2 mM; NaH_2PO_4 1.2 mM; $NaHCO_3$ 23 mM; glucose 10 mM). Rats were allowed to recover for one day before unloading.

2.5. Electrophysiological somatosensory mapping procedure

The electrophysiological mapping was performed on 33 rats (9 C, 12 HU, 5 IGF-1; 7 HU-IGF-1). The rats were anesthetized with sodium pentobarbital (60 mg/kg, i.p.). Animals of HU and HU-IGF1 groups were injected immediately after HU, and were not allowed to recover. If applicable, the acrylic cement block covering the cannula was removed cautiously. A craniotomy was performed to expose the region of the somatosensory cortex to be mapped. The dura mater was incised and resected. The cortex surface was bathed with warmed physiologic serum to the prevent drying. Electrophysiological recordings were performed to determine the extent of the hindpaw representation on the somatosensory cortex, as previously described [14]. Briefly, multiunit recordings were performed with tungsten microelectrodes (10 MΩ) in layer IV (depth: 700–1200 μm). The activity was amplified (x10k), filtered (bandwidth 0.3–10 kHz, model 1800 AC amplifier, AM-Systems), visualized on an oscilloscope, and delivered to an audio monitor. For each penetration site, the skin of the foot was hit with force-calibrated Semmes-Weinstein monofilaments (Stoelting Co.). If a light tactile stimulation of the hindpaw (<400 mg) specifically enhanced the neuronal activity, the recording site was considered as responsive; otherwise, it was considered as unresponsive. When responsive, the cutaneous RF and cutaneous sensibility threshold were determined. RF is defined as the paw region where tactile stimulation (400 mg) systematically enhanced neuronal activity, and threshold as the lowest stimulation force (8–20–40–70–160 mg) that enhanced neuronal activity. At the end of the mapping procedure, the cortical representation of the hindpaw was reconstructed by drawing boundaries to enclose the cortical sites responding to hindpaw stimulation. The hindpaw