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Injury induced dendritic plasticity in the mature central nervous system

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Injury to the mature central nervous system (CNS) induces a series of transient changes leading not only to death of neurons, but also to spontaneous rearrangement of the affected network. One of such pro plastic events, detected following injury, is an increased level of neurotrophins. Neurotrophins are a family of proteins involved in survival and outgrowth processes. The other one, more difficult to observe, is a change in the complexity of the dendritic tree, causing arborization or pruning, depending on many circumstances: i.e. lesion etiology. Subsequent therapies like enriched environment or locomotor exercise bring about a functional improvement, which was found to further increase the neurotrophin level and induced additional arborization of dendrites. Another important consequence of damage to CNS connections is deafferentation, shown to induce a down regulation of outgrowth inhibitors. Their suppression in turn may facilitate dendritic plasticity. Taken together, these factors may contribute to enhanced plasticity in the injured mature CNS. Thus the proper use of endogenously increased plastic potential seems to be important for design and optimizing therapeutic strategies. Further investigation of mechanisms involved in switching on plasticity may help to improve on existing therapies and find new ways to obtain better recovery following injury.

Key words: dendritic plasticity, injury, neurotrophins, exercise, mature CNS

INTRODUCTION

The feature most important for functioning of the nervous system is the ability to form proper connections between neurons, which allow successful communication within the network. Neuronal processes are divided into two categories: dendrites and axons. Dendrites are the main receivers of synaptic input and have more postsynaptic specialization than axonal processes (Fig. 1). Another attribute of dendrites are dendritic spines, processes a few microns in length, connected with excitatory synapse formation. The shape of the dendritic tree displays a high level of heterogeneity, which depends on a variety of factors. The most important factor is genetic determination, which can be modified epigenetically by external circumstances. Agents contributing to dendritic plasticity are neuronal activity, neurotrophic factors and the level of outgrowth inhibitors. A good example, which illustrates the influence of activity on dendrite formation, are the Purkinje cells of the Weaver mutant mouse. These mice are characterized by inaccurate migration of granule cells in the cerebellum (Bradley and Berry 1978). In effect they fail to make synapses on Purkinje cells. Nevertheless, Purkinje cells develop a dendritic tree, albeit much smaller and not well developed. Another factor which strongly influences morphology of dendrites is neurotrophic activity. The neurotrophin family includes the following proteins: neuronal growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4), present in higher vertebrates, and NT6 and NT-7, detected in fish (Lai et al. 1998). It was shown that BDNF induced the arborization in cultured neurons. Moreover, the synthesis of BDNF depends on neuronal activity, which drives a positive feedback

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regulating dendritic plasticity. In contrast, NT-3 neutralizes the effect of BDNF and causes an inhibition of dendritic development (McAllister et al. 1995, 1996). Other factors that influence dendritogenesis are outgrowth inhibitors such as myelin-associated glycoprotein (MAG) and Nogo, which were found to inhibit sprouting of dendrites in the mature CNS. Relatively high levels of trophic support and lower levels of outgrowth inhibitors are found during development of the CNS than in the mature system, favorable for plasticity. In the mature CNS most connections are formed and work properly, so the high level of outgrowth inhibitors are assumed to play a positive role, namely, they create a non-permissive environment for eventual sprouting, which could disturb a properly functioning network. However, some level of plasticity persists, important for normal activity, and for processes connected with learning and memory formation (Bliss and Collingridge 1993, Martin and Morris 2002). Sometimes this relatively stable situation can be made more plastic even in mature CNS. One of the stimuli, which can induce it, is damage, which leads to destruction of existing connections. There are many experimental procedures to examine the mechanism induced by the injury. Most of them are the models of brain and spinal cord damage, imitating those which are frequently observed in clinics. In the case of brain damage, experimental lesions imitate stroke situations in humans, mainly related to the cortical deficits (Table I). Spinal cord lesions in rats and cats model injuries connected with the effect of car accidents; they may be divided into two main categories: partial damage allowing for spontaneous recovery, and total transection, which excludes this possibility. The first, acute change, induced by each kind of lesion, is connected with necrosis of neurons and fast degeneration of neu-

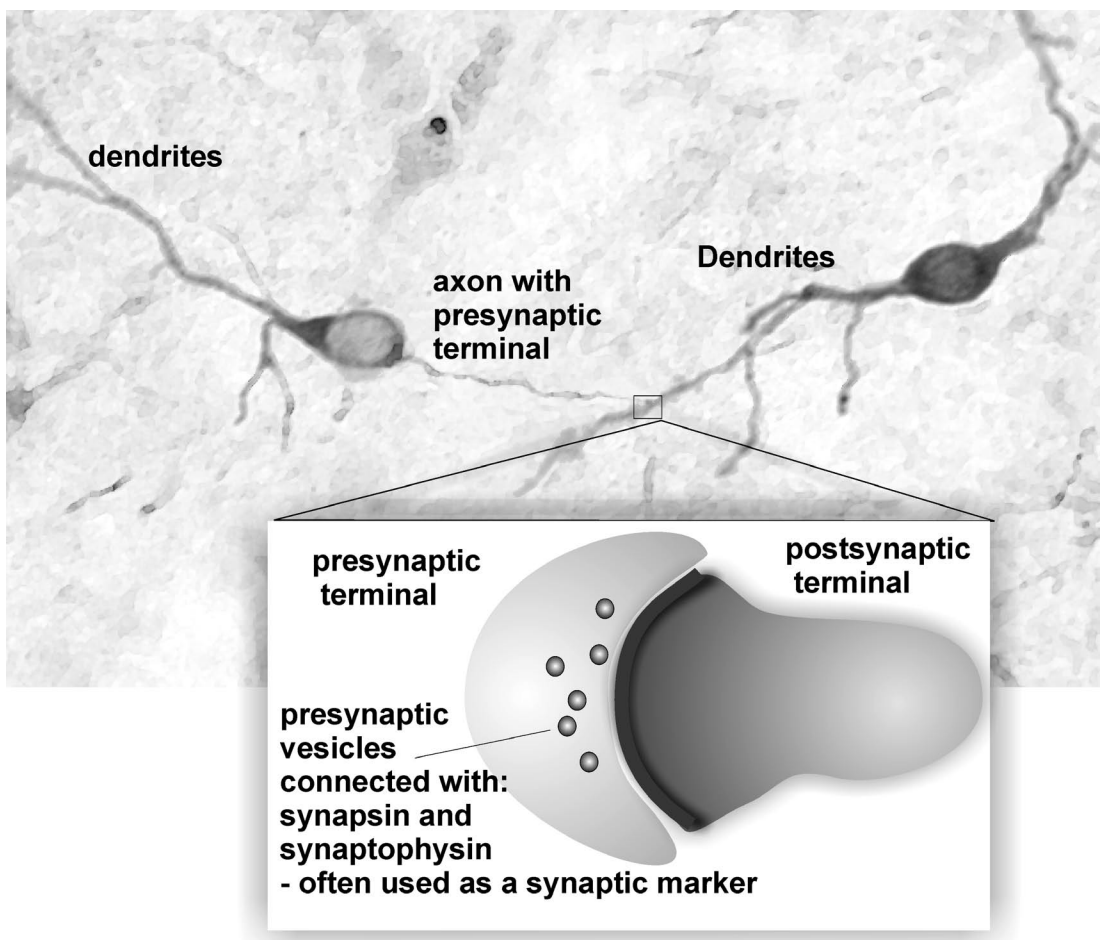

Fig. 1. Schematic illustration showing an axonal projection onto a dendrite of a neighboring neuron. Insert shows the characteristics of the synapse.

Table I

Different models of brain injury used as an animal model of human stroke

Animal model of stroke	Lesions	Early degeneration effect
Devascularization	Removal of vasculature that supplies blood to sensorimotor area of cortex	Necrosis of ischemic region
Middle cerebral artery (MCA) occlusion	Temporal occlusion of MCA	Broad necrosis of areas perfused by MCA
Electrolytic	Electrolytic coagulation of defined cortex area	Necrosis of coagulated area
Adsorption	Removal of defined cortical tissue by suction	Necrosis of peri-infarct areas
Photothrombotic lesion	Damage of vasculature by exposure to light, which excites the photosensitive dye administrated prior to the surgery	Necrosis of ischemic region

ronal processes in the center and in the proximity of the injury. The loss of tissue is then gradually extended to neighboring areas, where massive apoptotic death is observed (Sulejczak et al. 2004). Plastic phenomena frequently described in the second phase following the lesion are modifications of the dendritic tree and synaptic contacts, which are often preceded by upregulation of neurotrophic factors (Nieto-Sampedro et al. 1982, Sulejczak et al. 2007) and/or changes in the levels of outgrowth inhibitors (Chytrova et al. 2008). Although the timing and presence of secondary events differs between affected structures, i.e. cerebral cortex or spinal cord, and depends on the kind of lesion, the general consequence is an enhancement of spontaneous plasticity, which can facilitate functional recovery induced by applied therapy.

INJURY AND DENERVATION-RELATED PLASTICITY

Dendritic plasticity in the cortex following injury

Several studies have shown that cortical injury by itself enhances the plastic potential of cortical dendrites in peri-infarct and in contralateral, unaffected homotopic areas (Kolb and Gibb 1991, Jones and Schallert 1992). Jones and coworkers for the first time showed that small unilateral electrolytic motor cortex lesions induced a growth of dendritic arbor in the layer V pyramidal neurons in the motor cortex contralateral to lesion. Maximum arborization observed over two weeks post lesion (Fig. 2) was followed by partial elimination, or pruning, of dendritic processes. The arborization effect was subsequently found in different models of cortical injury (Biernaskie and Corbett 2001, Gonzalez and Kolb 2003). Microarray studies confirmed, that the cerebral cortex in the perilesion area and the contralateral areas reveal an increased expression of mRNA for activity regulated cytoskeleton associated protein (Arc), which seems to be connected with activity-dependent plasticity of dendrites (Keyvani et al. 2002).

Dendritic changes are functionally meaningful and associated with behavioral performance (Fig. 2 B). It was proven by Jones and Schallert (1992, 1994), that the overgrowth of dendrites was strictly correlated in time with over-reliance on the ipsilateral unaffected forelimb for postural and exploratory movements. Over-reliance on the unaffected forelimb was accompanied by disuse of the affected forelimb contralateral to the lesion (Fig. 2 A,B). The functional improvement of the affected forelimb was paralleled with pruning of dendrites in the unaffected cortex. To evaluate

whether morphological plasticity in the motor cortex depends on the maintenance of sensory stimulation, the ipsilateral (unaffected) forelimb was immobilized for the period critical for arborization (until three weeks post lesion). This resulted in no outgrowth effect (Jones and Schallert 1994), providing strong evidence that post injury dendritic arborization is entirely dependent on maintenance of the ipsilateral (unaffected) forelimb activity. On the other hand, the pruning phase was paralleled with improvement of the affected contralateral forelimb. Thus, to examine whether pruning of dendrites is directly related to the improved performance of the affected forelimb, the pruning phase was prevented pharmacologically by administering a NMDA receptor antagonist (such as MK801). In effect the behavioral impairments persist. However, discontinuing MK801 one month post-lesion resulted in functional recovery of affected forelimb

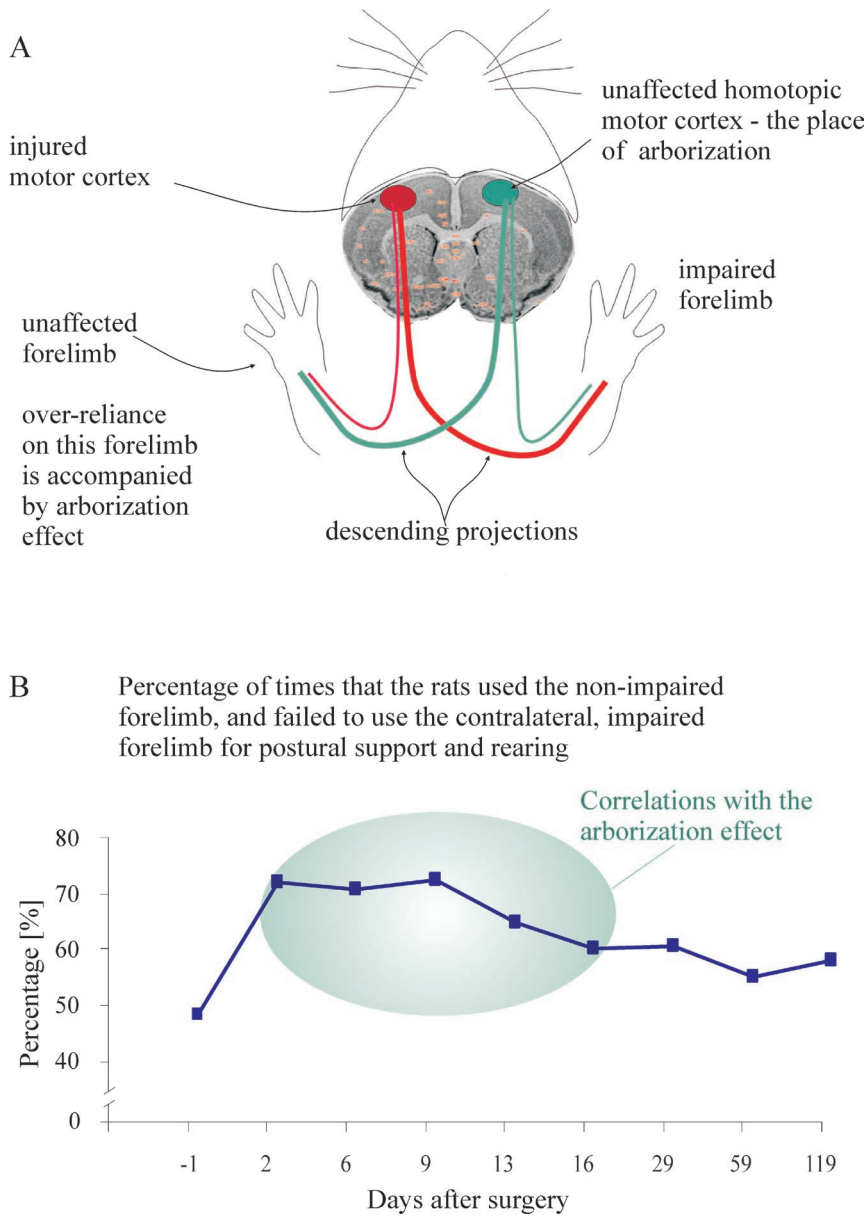

Fig. 2. (A) Schematic representation of descending corticospinal tracts of the injured motor cortex (red) and unaffected homotopic area (green). The thickness of the lines indicates the relative number of fibers that comprise the descending tracts. (B) Graph showing the time course of spontaneous behavioral changes after the unilateral cortex lesion, which are accompanied by changes in dendritic morphology. The arborization of the dendritic tree is paralleled by over-reliance on the unaffected ipsilateral forelimb. The pruning of dendrites is related to the postural support improvement (See Jones et al. 1992, 1994).

with upregulated dendritic arborization (Kozlowski and Schallert 1998). Summarizing, the dendritic arborization seemed to be related to increased activity of the unaffected forelimb. In contrast the pruning phase was not directly correlated with functional recovery of affected forelimb. Not all experimental evidence supports the result obtained by Jones and colleagues (Jones and Schallert 1992, 1994, Jones et al. 1996) (see Table II). Indeed, a number of studies revealed different results concerning the lesion-induced dendritogenesis and its connection with spontaneous recovery (Kolb and Gibb 1991, Jones and Schallert 1992, Prusky and Whishaw 1996, Bury et al. 2000, Churchill et al. 2004). It was shown by Gonzalez and Kolb (2003), that dendritic changes initiated by brain injuries depends on the lesion etiology, the brain region and the layer location of analyzed cells. They compared the effects of devascularization, middle cerebral artery (MCA) occlusion and tissue aspiration. The layer V pyramidal cells in the undamaged and injured hemisphere showed increased dendritic length following devascularization, whereas a decreased dendritic length has been found exclusively in the hemisphere ipsilateral to an aspirative lesion. In the latter type of injury there was an increase in spine density, whereas no spine changes were found in neurons following devascularization. No relation between dendritic plasticity and behavioral improvement in these injury models was found (Gonzalez and Kolb 2003). Thus, although the presence of plastic changes triggered by cerebral cortex lesion has been well documented, the triggering factors and mechanisms, which determine the direction of changes towards dendrite arborization or retraction are not clear. Also, a correlation between functional improvement and reorganization in dendrite morphology is equivocal.

Table II

The effect of different cortical lesions on dendritic plasticity

Models of cerebral cortex lesion	Changes in dendritic morphology	
	Contralateral hemisphere	Ipsilateral hemisphere
Electrolytic	Arborization	No changes
MCA occlusion	No changes	No changes
Aspiration	Pruning	No changes
Devascularization	Arborization, elongation	Arborization

Dendritic spines and synapses

Recent years brought a development of the *in vivo* two-photon imaging technique (Misgeld and Kerschensteiner 2006, Lonser et al. 2007), which has allowed researchers to broaden studies for real time observation. Brown and coworkers (2007), using this method, found that dendritic spines become exceptionally malleable after a stroke. This was manifested by a significant increase in dendritic spine formation that persisted for up to 6 weeks, and was specific to the peri-infarct cortex (Brown et al. 2007). This finding is in line with other reports showing that stroke induces significant changes in the functional representation of peri-infarct regions (Dijkhuizen et al. 2001, Wei et al. 2001). The time course of enhanced spine turnover is similar to the course of behavioral recovery found for forepaw function by Jones and Schallert (1992) (Shanina et al. 2006). There has been no such study for the contralateral, non injured hemisphere. As such, it would be interesting to know if plastic changes take place also in that area.

Changes in dendritic morphology observed due to injury are concomitant with synaptic modification (Stroemer et al. 1992). Outgrowth of dendrites is correlated with axonal rearrangement. It has been proven histochemically, that markers of axonal sprouting and of presynaptic terminals such as GAP-43 and synaptophysin, respectively, become progressively enriched in the peri-infarct cortex (Stroemer et al. 1993, 1995). The microarray data revealed similar changes both in the injured and the unaffected homotopic cortex. There was an upregulation of synaptic markers like Synapsin 2A, Synaptotagmin-I and Neuroglycan C precursor (Keyvani et al. 2002), which is a transmembrane chondroitin sulfate proteoglycan involved in synaptogenesis and formation of neuronal networks (Aono et al. 2000, Inatani et al. 2000). Also the electron microscopic analysis provided evidence that dendritic arborization in the contralateral (undamaged) hemisphere is connected with an increase in the number of synapses per neuron (Jones et al. 1996). Although a

causal link between (1) increased synaptogenesis, (2) dendritic spine formation, (3) changes in complexity of the dendritic tree and (4) recovery of function has not been clearly established, it is tempting to speculate that the changes in the rate of spine formation during recovery may define a critical period for which the brain may be particularly amenable to therapeutic interventions.

Dendritic plasticity in the spinal cord following injury

Although dendritic plasticity was examined mainly in the cerebral cortex because of its well documented rearrangement capabilities (McCandlish et al. 1996, Calford 2002), other CNS structures also undergo plastic adaptations following a lesion. One of the structures investigated extensively is the spinal cord. Unlike cortical injuries, spinal cord injuries were reported to cause shrinkage, rather than arborization, of motoneuronal dendrites. It was shown by Bose and colleagues, that incomplete spinal cord contusion results in a 37% decrease of the total number of dendrites as compared with those of normal controls (Bose et al. 2005). Simplification of the dendritic tree was found to be accompanied by synaptic rearrangement. It was also demonstrated that low thoracic hemisection caused a transient down regulation of synaptophysin immunoreactivity in the injured ventral horn (up to 3 weeks) and increased gradually to reach the control level at 3 months after the lesion (Nacimiento et al. 1995). Functionally, these changes possibly indicate changes in synaptic coupling to interneurons, and descending projections. On the other hand, partial spinal cord lesions usually lead to spontaneous functional recovery (Daly et al. 1996, Raineteau and Schwab 2001). An improvement was found to be correlated with upregulation of another synaptic marker, synapsin-I (Gulino et al. 2007). Thus, in the first phase after injury the synaptic connections seem to be eliminated, but later on they can be enriched in an activity dependent manner. Another, unique form of dendritic plasticity, observed due to proximal axotomy is a sprouting of *de novo* axons from distal dendrites. However, it was found and well described for motoneurons only (Linda et al. 1992a,b, Rose et al. 2001). More recently Fenrich and coworkers (2007) performed experiments to verify whether other spinal neurons i.e. interneurones, can respond to axotomy in a similar way. The authors cut the cervical spinal cord longitudinally to isolate left and right halves of spinal cord. Hence bilaterally, interneurones which innervate contralateral motoneurones underwent axotomy (Fig. 3 A,B). The somata of axotomized interneurones were identified by the presence of immunoreactivity for the axonal growth-associated protein-43 (GAP-43). The authors showed for the first time that the investigated interneurones had developed *de novo* axons that emerged from distal dendrites or a long axon-like process that projected directly from the soma or a very proximal dendrite. Some of these fibers projected through the lesion (Fig. 3C) and formed button-like swellings, which indicate presynaptic terminals. These results suggest that dendrites of axotomized spinal interneurons have not only a potential to form new connections, which can be crucial for spinal network rearrangement due to the lesion, but also may form morphologically distinct fiber structures which substitute the lost ones.

To date, there is only one but solid study that documents dendritic plasticity after complete spinal cord transection. Similarly to the hemisection lesion, complete transaction of the spinal cord caused a retraction of motoneuron dendrites (Gazula et al. 2004).

Altogether the data show that a spinal cord lesion activates an intrinsic potential towards dendritic and synaptic reorganization, which at least in the case of partial lesions is paralleled by functional improvement.

CNS lesion and neurotrophins

Neurotrophins are molecules that are extremely important for neuronal plasticity (Lessmann et al. 2003). Many researchers have designed experiments to investigate whether plasticity observed after injury is somehow associated with these molecules. Injury of the developing CNS, which is characterized by higher neurotrophin levels, than the mature one, resulted in much better recovery (Saunders et al. 1998). The breakthrough was a study by Nieto-Sampedro and coauthors published in Science in 1982, who showed the trophic potential of the adult brain after injury. The authors put gelfoam into brain wound cavities of young and adult rats. In that way, fluid secreted by the neighboring nervous tissue was trapped in gelfoam, collected and its neurotrophic activity was tested on cultured neurons. The experiment proved that brain wounds of both

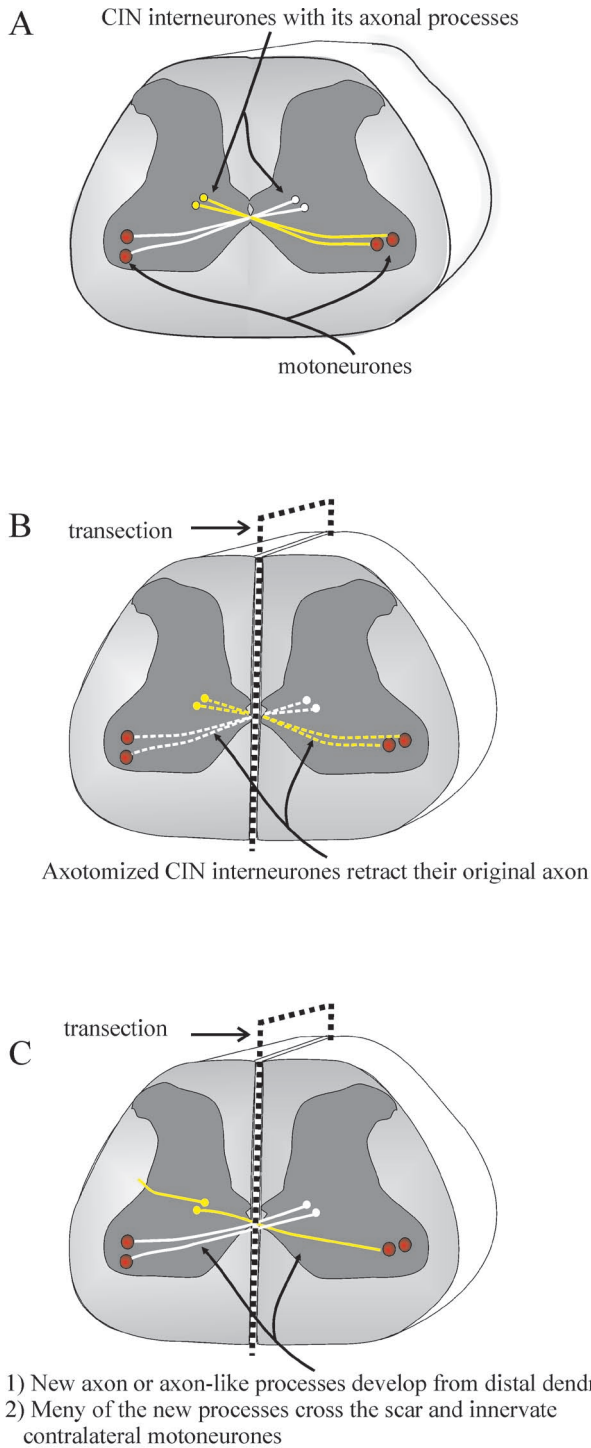

Fig. 3. Longitudinal transection of spinal cord causes axotomy of commissural interneurons (CINs), followed by development of a new axon from distal dendrites. (A) CINs normally innervate contralateral spinal cord motoneurones. (B) Longitudinal spinal cord transection causes axotomy of CINs. (C) Axotomized CINs spontaneously develop a new axon from distal dendrite. Note that many new fibers cross the scar and reinnervate motoneurons (see Fenrich et al. 2007).

young and adult animals accumulated neurotrophic factors and that this activity was enhanced in the first few days post injury (Nieto-Sampedro et al. 1982). Thus, enhanced trophic stimulation was found to be present not only in the developing but also in the mature CNS. Further investigation revealed that upregulated neurotrophins included NGF and BDNF but not NT-3 (Lorez et al. 1989, Yang et al. 1996, Sulejczak et al. 2007). Moreover, the elevated level of NGF was found not only in the lesion proximity but also in the contralateral intact homotopic cortex (Lee et al. 1996). That latter finding explains, at least partly, the dendritic arborization effect observed in the contralateral, undamaged hemisphere after the lesion. Neurotrophic factors exert their function via the high and low affinity receptors. Combinations of those receptors on the target cells are essential for neurotrophic action. Therefore, many studies were designed to elucidate the responses of neurotrophic receptors due to injury. It was shown, that after focal cortical and hippocampal lesion there was fast but transient (in a matter of hours), elevation of tyrosine kinase B (TrkB) and tyrosine kinase C (TrkC) – the receptors for BDNF, NT-4 and NT-3 respectively (Mudo et al. 1993). Taken together, these data point to an enhancement of sustained trophic support more by the upregulation of neurotrophin levels rather than by changes in their receptors. This is also supported by the results on the effects of injury at the spinal cord level which induced a downregulation of high affinity neurotrophic receptors (Liebl et al. 2001, Widenfalk et al. 2001). On the other hand, an analysis of mRNA levels for all neurotrophins due to the spinal cord injury showed that NGF and GDNF mRNA were upregulated in meningeal cells adjacent to the lesion while BDNF mRNA expression increased in neurons. NT-3 mRNA was not detected either in normal or transected spinal cord (Widenfalk et al. 2001). Reviewed data indicate that neurotrophic systems in both the brain and spinal cord actively react to injury, possibly in an activity-dependent manner. It was shown that unilateral cortex lesions induce disinhibition, which in turn causes facilitation and enhanced activation of both hemispheres (Liepert et al. 2000).

Dendritic plasticity after deafferentation

Structural rearrangements in the CNS underlie reorganization of cortical sensory maps in the adult brain in response to sensory deafferentation (Florence and Kaas

1995, Florence et al. 1998). Following peripheral nerve injury, cortical fields with intact inputs expand into deprived neighboring territory in the primary somatosensory cortex very soon after deafferentation (Merzenich et al. 1983, Kolarik et al. 1994). The barrel field has a very well defined cortical representation for vibrissa, hence it is a useful model for cortical plasticity examination. An elegant example illustrating morphological changes occurring due to deafferentation was the experiment done by Tailby and coworkers (2005). They showed that pyramidal cells in the barrel field normally navigate their dendritic arbors toward the center of their associated barrel. The situation was different after the vibrissectomy. Branching complexity was reduced at the center of the barrel and more branches appeared in the opposite direction. However, overall dendritic lengths, arborization areas, and spine densities were in the normal range (Tailby et al. 2005). Thus, the lack of proper activation induced morphological changes of dendrites, which began to turn toward normally active areas and may have formed new connections.

Recently, the molecular events underlying this reorganization process has been analyzed. It is documented that the CNS milieu is rich in myelin associated proteins (Varga et al. 1995), which are connected with an inhibition of sprouting (Bandtlow et al. 1990). On the other hand, several factors in the brain, such as BDNF were described to act in the opposite way. Hence, Endo and coworkers focused on these two families of proteins and investigated if deafferentation influence them. To answer the question they monitored both, plastic changes in the somatosensory cortex and the mRNA levels for myelin associated inhibitors: NgR, LINGO-I and neurotrophin BDNF, following spinal cord transection. The FMRI examination of cortical plasticity showed the extension of original forelimb territory to occupy the deprived hindlimb area. At the same time, the mRNAs for NgR and LINGO-1 were down-regulated in cortical areas deprived of sensory input and in the adjacent cortex from early after injury, while BDNF mRNA was up-regulated. Interestingly, the observed changes were more evident in the superficial layer of the cortex, and not, as could be expected, in axotomized neurons in layer V (Endo et al. 2007). It suggests that axotomy *per se* is not an inductor of described reorganization. Observed plastic rearrangement might be connected rather with decreased afferentation of upper cortex layers.

DIFFERENT THERAPEUTIC APPROACHES TO THE INJURED CNS

One of the strategies known to induce CNS plasticity is to rely on exploratory and motor behavior, such as environmental enrichment and forced physical exercise. These activities have been shown to lead to functional improvement after CNS injury and are known to upregulate endogenous factors involved in plasticity in both, injured and noninjured animals (Biernaskie and Corbett 2001, Leggio et al. 2005, Ghiani et al. 2007, Ploughman et al. 2007). It was shown for instance, that both treatments applied to the uninjured animal, increase the level of BDNF in the brain (Oliff et al. 1998, Dobrossy and Dunnett 2006). In the spinal cord, an induction of BDNF expression was observed only due to the locomotor exercise (Macias et al. 2002, Skup et al. 2002). A similar situation was described for dendritic arborization. Enriched environment was found to be effective in stimulating dendritogenesis in the brain (Kozorovitskiy et al. 2005), likewise locomotor exercise in spinal cord, of normal uninjured animal (Gazula et al. 2004). It was described in the preceding paragraph that injury by itself can upregulate the levels of BDNF and induce synaptic and dendritic plasticity. This raises the question, what would be the resultant outcome of postinjury behavioral treatments on dendritogenesis, BDNF protein level and their denotation to functional recovery?

Effects of behavioral therapy on injured cerebral cortex

Confirming previous observations obtained for injured cerebral cortex, Bienarskie and Corbett (2001) showed that focal injury in the motor cortex resulted in arborization of the basilar dendritic tree in layer V of the unaffected cortex in the hemisphere contralateral to the unilateral lesion. In addition to this effect, rearing in an enriched environment combined with challenging a skilled forelimb task (animals were required to use an impaired forelimb for climbing on a platform and to successfully retrieve and eat pellets) enhanced total dendritic length. Further morphological changes were paralleled with improved performance in a skilled behavioral test. In contrast, ischemically injured animals reared in standard conditions remained significantly impaired

(Biernaskie and Corbett 2001). Thus, the enriched environment increased the arborization effect of injury and substantially improved the behavior compared to the level of spontaneous recovery.

Several studies were aimed to elucidate whether behavioral treatments which induced dendritic plasticity are accompanied by changes in trophic support. BDNF is the neurotrophin which is particularly sensitive to exercise stimulation. It was demonstrated that locomotor exercise upregulates the mRNA for BDNF and the level of BDNF in the hippocampus and motor cortex of normal rats (Neeper et al. 1996, Oliff et al. 1998). On the other hand, the level of BDNF was enhanced after focal cortical injury in the lesion proximity and related areas (Kokaia et al. 1998, Sulejczak et al. 2007). Thus the Corbett group decided to test the endurance of exercise required for optimal elevation of BDNF, needed during stroke rehabilitation. They compared the effect of a single episode of regimens of locomotor exercise: moderate walking, running, longer walking - forced on the treadmill, and long voluntary running (12 hours) in rats after a focal motor cortex injury. The experiment showed that BDNF increased in the lesion's proximity and that further exercise did not enhance it. In contrast to the ipsilateral, injured side, the elevation, due to locomotion, took place in the contralateral uninjured hemisphere. The highest increase was induced by moderate exercise (Ploughman et al. 2005). Moreover, the same authors demonstrated recently that BDNF elevation due to moderate exercise was the highest immediately after the training session and after two hours it decreased to the control level. In contrast, BDNF upregulation due to voluntary running was lower, but persisted up to two hours. Thus an outgrowth of dendrites in the hemisphere contralateral to the lesion, extended by enriched environment and locomotor exercise, can be related to the quantity of neurotrophin liberated due to enhanced activity. Those quantities repeated regularly may be responsible for triggering changes in the morphology of dendrites.

Additional therapeutic strategies rely on administration of exogenous factors, which influence neuronal plasticity. One such treatment is administration of antibodies (Ab) neutralizing outgrowth inhibitors. For example, the NogoA Ab treatment causes functional benefit in challenging skilled forelimb tasks after motor cortex injury (Papadopoulos et al. 2002). More recent work by the same author (Papadopoulos et al. 2006) has demonstrated that functional improvement observed earlier was paralleled with outgrowth of both basilar and apical dendrites, and with increased spine density in layer V pyramidal neurons of the motor cortex contralateral to the lesion. Moreover, analysis of the dendritic tree in the cortex unrelated to the injury (i.e. visual cortex) showed no such changes, thus the arborization effect was restricted to the contralateral motor cortex only. Thus it would be interesting to see if rehabilitative strategies in combination with i.e. neutralizing outgrowth inhibitors can increase observed positive changes. So far, there is no data on this subject. However, it was shown, that locomotor exercise down regulated the level of myelin associated proteins in the ipsilateral hippocampus of rats after traumatic brain injury (Chytrova et al. 2008). Together these data point to formation of a more permissive milieu for dendrites and synaptic plasticity owing to enrichment in neurotrophic factors, which can be further modulated by the subsequent treatments.

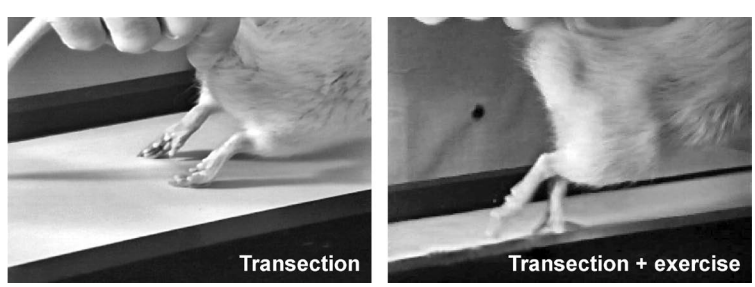

Fig. 4. Photographs of rats 4 weeks after thoracic spinal cord transection. On the left, an animal subjected to transaction and non-exercised. On the right, an animal subjected to spinal cord transection who received locomotor exercise. Note the improved stepping ability after the locomotor training (Czarkowska-Bauch 2007).

Effects of locomotor exercise on injured spinal cord

In contrast to the cortex, injury to the spinal cord and particularly transection, was never observed to induce any dendritic arborization. Indeed, spinal cord injury caused retraction of motoneuronal dendrites probably due to lack of afferentation from paralyzed limbs. However, in case of partial injury, spontaneous improvement was observed and rehabilitation by locomotor exercise brought additional benefit. Moreover, beneficial effects of exercise have been found even after complete transection (Fig. 4). The historical experiment, which proved it, was done in 1987 by Barbeau and Rossigniol (1987) who showed that cats with complete spinal cord transection, which underwent locomotion on a treadmill, began to perform stepping activity with the paralyzed hindlimb (Barbeau and Rossignol 1987). Thus, locomotor exercise alone seems to exert a strong effect on spinal cord circuitry and many researchers have since attempted to elucidate the cause of this promising phenomenon. However, there is only one experiment, which showed directly, that the observed functional improvement is accompanied by dendritic plasticity (Gazula et al. 2004). The authors stained the rat motoneuronal dendritic tree immediately after spinal cord transection. Subsequently rats underwent locomotor training. The experiment showed, that transection caused pruning of motoneuronal dendrites. After locomotor exercise the arborization of dendritic tree was higher, similar to arborization observed in uninjured animals (Gazula et al. 2004). Thus, the spinal cord lesion and subsequent behavioral treatment seemed to stimulate endogenous pathways, which lead to the dendritic plasticity, probably involved in beneficial effect of the locomotor exercise.

CONCLUSIONS

Damage to the CNS leads to a series of changes, which together make the affected region more receptive to plasticity. A very important factor is the upregulation of trophic cues in the lesion proximity, and in the case of the cerebral cortex, also in the contralateral homotopic area. Therefore, it is quite possible that neurotrophins trigger a phenomenon of dendritic arborization developing subsequently, and often observed in the contralateral, undamaged cortex. Moreover further behavioral treatments strongly enhance this effect. The question arises, why the changes triggered by the lesion and detected after the treatments, are also present in the contralateral, undamaged homotopic cortex. One explanation proposed by Jones and others (1994), suggested that it depends on enhanced activity of the unaffected forelimb. An intriguing possibility, not excluding the former one, is that deafferentation downregulates the level of outgrowth inhibitors, promoting dendritic and fiber growth, and that the homotopic cortex, albeit unaffected directly is in fact a partly deafferented area, due to destruction of the transcallosal connections with the injured region. The extent to which each of these factors contributes to awakening the dormant plastic potential is a matter of future research.

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