REVIEW

Neural plasticity and functional recovery of human central nervous system with special reference to spinal cord injury

D Wang¹ and T Sun²

¹National Spinal Injuries Centre, Stoke Mandeville Hospital (retired), Aylesbury, UK and ²Department of Orthopaedics, Beijing Army General Hospital, Beijing, China

Study design: Literature review.

Objective: To study the progress that has been made in neural plasticity for the past few decades.

Setting: United Kingdom/China.

Methods: An electronic search of relevant publications through PubMed was conducted using two key words: 'axonal regeneration' and 'neural plasticity'. The search included publications of the past three decades of all languages and of both animal and human studies. After confirmation of immense increase of publications on neural plasticity, reviewing of neural plasticity alone was conducted. The review covered only the most important and clinically relevant publications. For convenience of reading by busy clinicians, discussions focused on cellular and functional levels, and only the most investigated molecules were mentioned. The size of references is also planned to be concise rather than comprehensive into three digits.

Results: Neural plasticity is about memory and learning. The entire process of neural plasticity is presented in the sequence of (1) lesion-induced plasticity, (2) clearance of debris, (3) collateral sprouting (4) potentiation. The recent discovery and understanding of the important role of Chondroitinase in clearance of debris is discussed in detail.

Conclusion: Neural plasticity has enormous potentials in facilitating functional recovery. It is a realistic target than structural axonal regeneration at current level of neuroscience.

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Keywords: axonal regeneration; neural plasticity; functional recovery; role of chondroitinase; realistic target

Introduction

For decades, human race has been expecting quick success in structural repair of the damaged central nervous system (CNS), particularly the spinal cord. Unfortunately, such high expectation has not been materialised. However, some rapid functional recoveries were observed in chronic spinal cord injured persons who received cell therapy after their natural neurological recoveries had plateaued.¹ It is reasonable to suggest that such rapid functional recoveries may be attributed to neural plasticity rather than structural repair, which should take longer to appear and needs morphology to prove. Much work has been done on neural plasticity for the past few decades that has shed light on the mechanism behind natural recovery and outcome of therapy of nervous diseases and injuries. It seems timely and necessary to look into the progress in this regard, which constitutes the

purpose of this review. It has to be pointed out that this review is to offer some basic understanding of neural plasticity and functional recovery for clinicians instead of comprehensive knowledge for basic scientists who are already familiar with neural plasticity.

Materials and methods

A recent electronic search of relevant publications through PubMed was conducted using two key words: 'axonal regeneration' and 'neural plasticity'. The search included publications of the past three decades of all languages and of both animal and human studies. It was aimed at comparing the scale of increase of interest and efforts in the two fields. When the immense increase of publications on neural plasticity was confirmed, reviewing began to focus on neural plasticity alone. Because of the impossible amount of existing publications, this review could only cover the most important ones that are clinically most relevant. From the point of neuroscience, they offer latest fundamental understanding of the issue. Furthermore, discovery of a staggering

Correspondence: Professor D Wang, National Spinal Injuries Centre, Stoke Mandeville Hospital (retired), 11 Selkirk Avenue, Aylesbury, Buckinghamshire, HP19 9QD, UK.

E-mail: dajue.wang@bopenworld.com

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Figure 1 Comparison of increase of publications on 'axonal regeneration' and 'neural plasticity' for the past three decades.

number of molecules associated with neural plasticity has made describing even a part of them in a single article impossible. Hence, this review will be restricted to discussion at cellular and functional levels and only the most studied molecules will be mentioned in the context. Efforts were made to avoid bombarding clinicians with too many jargons of neurosciences.

Results

Increased trend in research on neural plasticity

The comparison of the numbers of publications on structural repair and neural plasticity has demonstrated a significant difference in the scale of increase between them (Figure 1). The results were stunning. The number of publications on 'axonal regeneration' had increased by 2.8-fold whereas that of 'neural plasticity' increased by 11.7-fold during the past three decades. The difference is highly significant ($\chi^2 < 0.001$). It clearly indicates that the idealistic approach of satisfactory structural repair seems to have changed. Instead of false hope or fantasy, after all, human race has come to accept the reality of current development of science and to adopt a more healthy and realistic approach of restoring limited but useful functions without major structural repair. The neural mechanism behind functional recovery without restoration of original structure is known as 'neural plasticity'. Neural plasticity is becoming an increasingly attractive topic for clinicians, neuroscientists and patients alike.

It is high time that clinicians were also armed with some basic knowledge of neural plasticity. By doing so, they can be more actively engaged in exploiting the potential of neural plasticity to enhance functional recovery. They can even be personally involved in basic scientific researches to further improve their understanding of neuroscience behind their clinical observation and management.

Figure 2 Phylogenetic ladder indicating palliospinal system responsible for somatomotor function is the most recently developed system (courtesy of Northcutt²).

General aspects of neural plasticity

When an animal suffers from a disease or injury, the nature intervenes and offers an automatic mechanism to repair the damage to its structure and restore its function for survival. The higher the animal, the less such mechanism works efficiently because of its sophistication developed in phylogeny. In the most highly developed system, the central nervous system (CNS) of the most highly developed animal (the human race), such mechanism is very limited. It is even more so for the highest developed nerve cell (Betz Cell) that controls human voluntary locomotion. This is determined by the law of evolution that the more developed the animal, the more complex its structure, and hence the more difficult to repair. Unfortunately, it is exactly the most highly developed part of the human CNS that most people expect to get repaired first. It is unrealistic to believe that this will happen soon. As a result, repair of human CNS, particularly the somatomotor system at the top of the ladder of phylogenetic development is the most difficult to achieve and so is restoration of its functions (Figure 2).²

Cajal³ concluded early last century that the neuron of the CNS could not regenerate. However, further development of neuroscience has offered new hope on the horizon. In the 1950s and 1960s, there were waves of interest in CNS regeneration. Two discoveries with far-reaching impact stood out as landmarks of neuroscience of that period. They were as follows:

1. Discovery of nerve growth factor by Levi-Montalcini in 1951.^{4,5}
2. Introduction of neuronal plasticity by Raisman in 1969.⁶

This review will only discuss about neural plasticity. Although Hebb and Konorski introduced the idea of neural plasticity at functional level, and Liu and Chambers observed sprouting earlier, details of sprouting based on experimental quantitative electron microscopic techniques for the study of synapses were not available until Raisman.⁶⁻⁹

Neural plasticity is a total concept of development and reorganisation of network of neurons and their environment. Interpreting it as some isolated processes cannot be

Figure 3 The hippocampus and amygdala of the limbic system (courtesy of <http://pubs.niaaa.nih.gov/publications/arh284/images/tapert.gif>).

farther from the truth. The morphological foundation of neural plasticity laid down in Raisman's publication has not changed for four decades and remains the cornerstone of the field. What was not mentioned in his article was the molecular mechanism of the process because at that time the DNA structure had not been discovered for long and molecular biology was yet to be fully developed. Extensive and intensive studies have been done since then and have been filling the gaps of molecular understanding of neural plasticity and resulting functional recovery.

Neural plasticity is all about adaptation to the environment for survival. It needs learning to do it and learning starts from memory.^{10,11} If John wants to travel from Point A to B, he needs to read the map and memorise the best possible route. If he can do it, it means he has learned how to travel. This is positive learning like in most cases of animal life. The development of functions of human CNS is a learning process based on memory. The short-term memory does not need protein synthesis whereas long-term memory does.^{10–12} The place where the necessary proteins are synthesised is the hippocampus (Figure 3), but they are stored elsewhere.^{13–15}

The sequence of events of the entire process of plasticity can be compared with the delivery of emergency care by rescue service to an earthquake zone and later follow-up by regular health system.

1. That a patient sustains a severe injury in an earthquake zone induces (lesion-induced plasticity) the need to call the service.¹⁶
2. The service responds to the call by sending out a rescue team to clear the ruins (clearance of debris) to make the injury site approachable.¹⁷
3. The ambulance has to navigate itself (sprouting-pathfinding) to reach the correct destination (sprouting-address selection).^{6–9}

4. The ambulance service only saves the patient's life (short-term potentiation), whereas the follow-up medical attention further improves the condition steadily (long-term potentiation).^{18,19}

The following parts of the review will be devoted to the entire process of neural plasticity in the above-mentioned order. All processes of plasticity involve molecular chemistry. Because of the impossible scale of the information, only major molecules will be discussed. Readers have to be reminded that almost all the findings were collected from very low animals on simple experimental models. It would be naïve and simplistic to think that these findings can be easily and fully translated onto human race without adjustment. Moreover, all processes in living organisms are cascades of continual events instead of any isolated and incidental ones.

Lesion-induced response

Lesion-induced response is often used to describe how neural plasticity is started. However, as mentioned above, plasticity is a normal response to the environment for survival and development in the first place. Therefore, it is the interaction between the organism and the environment and the term lesion-induced response reflects only the intrinsic and pathological part of the process. Any physiological response is the final common path of the entire organism or body. It can be affected and modulated by both intrinsic and extrinsic changes. The need for improvement of function can enhance plasticity. If there is no need for such improvement, for example, a non-paralysed limb is not restricted in a monkey, the recovery of the paralysed limb may not be substantial. If the non-paralysed limb is restrained, the recovery based on plasticity will be strengthened.¹⁶ In amblyopia, if not corrected early and the normal eye is allowed to occupy more space in the visual cortex, then late correction may not restore normal vision.²⁰ Hence, this process must be decided at higher level of the CNS that such a need exists. In spinal cord injury or other nervous diseases or injuries, the general perception is that physical exercises interpreted as a *need* force the limbs to work hard, thus improving their locomotion. Conversely, if there is no such need, the limbs' locomotion will not improve or improves very slowly and slightly if not totally wasted. Hence, the plasticity is not only lesion-induced but also *need-driven*.

For the peripheral nervous system, the response to damage is mainly reparative. Because of blind targeting, the severed axons may not find the correct opposite stumps and functional recovery is limited. In the CNS the lesion-induced response is a process, which is more destructive than constructive or reparative.

The primary instant response of the CNS to the lesion is further damage, particularly in the spinal cord.^{21–23} Despite the tremendous efforts made, scientists have failed to fully understand the secondary destructive process and all protection measures have not succeeded in preventing it from progressing.²¹ The use of mega dose of methylprednisolone recommended by the NASCAS II and III studies have

some benefit of improvement of neurology.^{23,24} However, the incidence of fatal and late complications is high. Therefore, some countries have abandoned its routine use.^{25,26}

The constructive or reparative process based on neural plasticity starts only three weeks later and may continue up to 18 months.²⁶ For other tissues, restoration of physical continuity by a scar is a healed lesion and functions can be restored. In CNS, where functions solely depend upon electrophysiologic conductivity, physical continuity without conductivity can only pose as a barrier to functional healing. Peripheral nervous system and the destructive process of the CNS are not topics of this review. Herein, only the late reparative process of the CNS based on neural plasticity is discussed.

Clearance of debris

This section involves some recent developments in the understanding of neural plasticity. After damage or death of a neuron or axon, its debris has to be cleared up before any reparative process can take place. In general, such job is carried out by blood-born macrophages. In the CNS, this process is not efficient probably because of the blood-brain barrier. In place, the microglia arrive within 5 h at the lesion site and begin to clear up the debris. Only when this is not sufficient, macrophages join in. This clearance process is much slower in the CNS than peripheral nervous system.

The role of microglia in clearing the debris from the CNS had not been properly understood and hence underestimated until a breakthrough in the 21st century when a family of well-known proteins for other purposes were discovered to possess the function of clearing debris of the CNS. It is known to be the chondroitin family.^{20,27}

The chondroitin family contributes to the entire process of animal development. It is a bit misleading to name it chondroitin, which is associated with cartilage. As animal embryonic development starts from skeleton, proteins that build the bone and cartilage are naturally precursors of almost everything. It is not surprising that they were found in the CNS. In fact this cartilage-associated protein has many functions other than cartilage development.

In normal condition, the chondroitin sulphate proteoglycans protect and guide axons and inhibit regeneration through its sulphated glycosaminoglycan chain (Figure 4).^{20,27} Chondroitin sulphate proteoglycans form the matrix of the CNS in three layers. The inner most layer is made of solid cartilage like substances known as the perineuronal net.²⁸ In case of injury or other damage, the perineuronal net hampers microglia or macrophages to clear the debris. An enzyme known as the chondroitinase produced by bacteria can break the barrier down and allow microglia and macrophages in to clear the debris.²⁰ Without this clearance, later phases of regeneration or collateral sprouting cannot take place. Hence, this process is not just about clearance but also about success or failure of the reparative and restorative process. NogoA and some other molecules have similar effect as chondroitin sulphate proteoglycans. Their mechanism is not fully understood.²⁰

Figure 4 The author's schematic showing (1) how chondroitin sulphate proteoglycans (CSPGs) compromises plasticity and regeneration; and (2) how chondroitinase reverses the process by digesting sulphated glycosaminoglycan (GAG).

Sprouting

Sprouting is early growth of axon that may or may not complete the journey of reaching the target neuron and restoring function. It is the key structural change that makes the plasticity happen to facilitate development of normal neurons and recovery of functions of injured neurons. Sprouting declines with age.²⁰

There are two types of sprouting: terminal and collateral (Figure 5). Terminal sprouting is part of a normal growth of an axon during embryo development or after injury where connection with the stump of the injured axon can be restored. This belongs to the topic of regeneration and hence, outside the scope of the current review that focuses only on neural plasticity. In case of injury when terminal sprouting of the original axon fail to reach the target neuron, collateral sprouting of neighbouring axons steps in. In this review only collateral sprouting is discussed. Such sprouting always occurs at the site of the Node of Ranvier and hence also known as node sprouting.¹⁵ There must be a very complex mechanism of initiating collateral sprouting involving a series of molecules. This mechanism is not yet fully understood.

The most basic molecule involved in facilitating sprouting is actin, which is also seen in muscles.²⁹ The growth of axon starts from its growing tip known as the growth cone (Figure 6) (http://en.wikipedia.org/wiki/Growth_cone).^{29,30}

Figure 5 Two types of sprouting: terminal and collateral (nodal). Courtesy of Levitan.¹⁵

Figure 6 The growth cone of axon. On the left, the cones stretch out like feet. On the right, a webshape cone is formed with further growth. (Cropped photos. Courtesy of http://www.cdb.riken.go.jp/jp/04_news/annual_reports/2004/webhelp/lab1_07h1fig1s.jpg and <http://www.acsu.buffalo.edu/~ccohan/icons/dic.jpg>).

Other molecules involved are divided into three groups.²⁹

1. *Growth factors or nerve trophic factors*: 43 kDa growth associated protein (GAP-43), brain derived neurotrophic factor (BDNF) and neurofilament (NF).
2. Cell adhesion molecules
3. Guidance molecules

The first group galvanise and enhance axonal growth whereas the latter two groups are the navigation system of sprouting (pathfinding). The adhesion molecules can adhere physically to the target neurons whereas the guidance molecules cannot. The mechanism how guidance can take effect in the latter is not fully known. It is suggested to be change in the rate of polymerisation of actin at the site of interaction. Molecules of Groups 2 and 3 and their receptors are summarised in Table 1. Accurate transmission of signals to the correct target neuron depends upon match of acting molecules and receptors. This process is termed address selection.

Potentiation and functional recovery

Molecular chemistry is only part of the story of plasticity. For functional recovery to happen, molecular chemistry has to

Table 1 Cell adhesion and guidance factors and their receptors

Adhesion molecules	Receptor	Guidance molecules	Receptors
Substrate molecules Fibronectin Laminin	Integrins	Semaphorins Netrins	Neuropilins, plexins UNC-40, <i>Caenorhabditis elegans</i> DCC, vertebrates Frazzled (<i>Drosophila</i>) UNC-5 (repulsive)
Cell adhesion molecules (CAMs) Cadherins	(CAMs) Cadherins	Nogo Ephrins	Unknown EphA & EphB receptors

Figure 7 The role of synthesis of C-fos and C-jun in neuroplasticity (Courtesy of Levitan¹⁵).

be translated into electro-physiological activities, wherein, in addition to proteins, ions (Na^+ , Ca^{2+} , Mg^{2+} and Li^+) are involved.³¹

When the target neuron receives short frequency of stimuli, there is only facilitation of an event. The effect does not last long and is not stored or memorised in the CNS to be enhanced or repeated later. It does not trigger protein synthesis either. Such event is known as short-term potentiation.^{31–35}

If the stimuli repeat themselves many times, they give rise to synthesis of proteins to be stored in the CNS as memory and the effect will last. This process is known as long-term potentiation.^{31–35} This is probably the most important end result rehabilitation professionals would like to see and exploit, such as intensive and extensive physical training leading to functional recovery.

The molecular foundation of such memory is two cellular proto-oncogenes, C-fos and C-jun (Figure 7).¹⁵ They belong to the immediate early gene family of transcription factors. They link growth factors with some specific proteins.

Discussion

Functional recovery after a supposedly irreversible lesion in the human CNS is a new memorising and learning process based on neural plasticity. This process can be normal or

enhanced. The normal process represents the natural history of recovery. However, such process can be enhanced by chemical (pharmaceutical), physical (mechanical and electrical) and biological (molecular and/or cell therapy) means in isolation or combined. All these methods have proven to be effective in animals, whereas their efficacy of statistical significance in humans remains to be proven. The difficulty lies in the involvement of multiple factors interacting upon each other in clinical setting. This makes the clinical trial extremely complex. Picking out a single method as effective is a tremendous challenge if not an impossible task.

Although it is known that plasticity is behind the functional recovery, the exact route the new reorganised circuitry takes is not clear. This process is likely to be executed through interneurons.³⁶ Probably there is no need for clinicians to dig deep to know it because there may be no fixed pattern and the route may vary from case to case. The rationale behind such a suggestion is that the reorganised circuit can take any easiest route to reach the target, similar to the rule that fluid follows the path of least resistance in hydrodynamics. It is also known that the type of neurons that spoutings target at is interneurons. This suggests that the reorganised circuitry probably involves the reticular formation instead of a small number of phylogenetically well-developed long tracts. Then the options open for reorganising the circuitry are mathematically astronomical and the connections are more than trillions. This offers the flexibility of an enormous amount of possible alternative routes. If there is no flexibility, there is no plasticity.

It is easy to understand that in incomplete injury, the reorganised circuitry can negotiate a way through the injury site through residual paths and finally reach the target neurons. This would not happen in complete injury. However, some rhythmical movements below a complete lesion in animals were observed in as high as rodents and cat. There must be a reorganising mechanism that can produce this rhythmic instead of chaotic movements. This mechanism is commonly known as the central pattern generator.²⁹ Such a mechanism may not be exactly located microscopically and how it is reorganised remains to be known. However, at macroscopical level, it can be understood that survival is a natural mechanism at all levels of life, whether whole body, system, organ, cell or molecule. It is possible that learning can be achieved at lower levels of the CNS, whereas in higher animal, particularly in human race, it requires involvement of higher structures like brain.

Attempts have been made in humans to reproduce some useful rhythmic movements in complete injury to simulate ground walking by step training on treadmill, particularly with body weight support or suspension.³⁷ Such attempts ended with little success.

In incomplete injury, comparing results between step training and ground walking did not show statistical significance.³⁸ This might be because of the complexity of clinical trials where too many factors are involved. This lack of statistical significance is often interpreted as invalidity of the method concerned. It is worth noting that statistical significance differs from clinical importance. Statistics is all about

probability or reproducibility of certain results in a categorised cohort. It is not about certainty to determine whether a method is valid or not. It cannot be more clear as Lang and Secic³⁹ point out: 'a *P*-value is not proof of anything.'

Although axonal regeneration of human spinal cord after injury has yet to be proven, most agree that promoting functional recovery through various rehabilitation techniques based on neural plasticity is viable. Researches in the past three decades have revealed many of the exact mechanisms of neural plasticity. This has been briefly covered in the review.

Huge controversies exist regarding cell therapy for spinal cord repair. It might be worth noting the first author's personal observation of more than 60 patients with olfactory-ensheathing cell transplantation. It suggests that the limited functional recovery after the procedure is the result of neural plasticity rather than regeneration. The basis of such a suggestion is that most patients who had received the procedure had increased sweating only a few hours post-operatively. This could not possibly be regeneration in time perspective alone.

Lack of basic knowledge about evolution leads to the unrealistically high expectation that human spinal cord can be structurally repaired in the near future that a complete paraplegics can stand up voluntarily. People who think so ignore the simple fact that it took 600 million years for a primitive animal to develop into human race.⁴⁰ Standing up requires the most lately developed Betz Cell (pyramidal cell). Without researches revealing the secret of this colossal phylogenetic gap there is little evidence that successful repair can be achieved in the near future. Trying individual cell for transplant by chance sounds like lottery and does not work well in serious science. So far, almost all experiments on repair of spinal cord with limited success are done on rodents, which are 4.5–15 million years apart from human race.⁴¹ These results could not possibly be translated into human success in a short space of time even with intensive scientific efforts.

Wishful thinking may kill science and patients.

Further readings

Unlike this review that discusses neural plasticity in a concise way accessible to general physicians without a solid background of neuroscience, the following two articles that are not included as references are excellent comprehensive reviews on the subject. Both have an extensive literature citation of more than 300 articles. They are recommended only for those who want to seriously expand their knowledge on neural plasticity. The first one is about details of researches before the importance of chondroitin sulphate became known.

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2. Galtrey CM, Fawcett JW. The role of chondroitin sulfate proteoglycans in regeneration and plasticity in the central nervous system. *Brain Res Rev* 2007; **54**: 1–18.

Conflict of interest

The authors declare no conflict of interest.

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