NEUROPLASTICITY AND ITS IMPLICATIONS ON REHABILITATION

Victoria Sciberras MSc S.R.O.T.

For many years following the discovery that specific areas in the brain are related to specific functions in the body, rigid concepts were formed regarding the central nervous system (CNS) being "hard-wired" or fixed and unchanging. This concept of specificity excluded reorganisation potential in the CNS, and therefore no recovery was expected following a CNS lesion, except that due to the resolution of local factors, such as oedema and tissue debris (Kelly, 1985; Bach-Y-Rita, 1989).

Reasons for the failure of axonal regeneration in the CNS of higher animals are still much debated. Since the last decade, experimental evidence has shown that the CNS is capable of repair and regeneration to a much higher degree than was previously believed (e.g. Raisman, 1969; Carlen et al, 1978; Aguayo & David, 1981). Results from these studies showed that following a lesion, the CNS undergoes both structural and functional changes via a reorganisation of its connections, known as plasticity. Bishop (1982d) defined plasticity as the 'morphological and functional changes occurring in the CNS in response to neural lesions'. However, this essay, will debate this definition, in that not all structural changes lead to significantly measurable functional changes.

Another definition given by Brown and Hardman (1987) explained plasticity more precisely, describing it as 'the ability of cells to alter any aspect of their phenotype, at any stage of development, in response to abnormal changes in their state or environment'. This definition demonstrates a dynamic, potentially adaptable CNS.

This essay will analyse the various experimental evidence which identify certain mechanisms of CNS plasticity through recovery phenomena following lesions of the CNS, such as sprouting, denervation supersensitivity, unmasking of previously dormant pathways and others, which will be defined under the respective sections. These mechanisms contradict the traditional belief that the adult mammalian CNS is incapable of repair and regeneration.

The last section of the essay briefly discusses the possible implications of the above-mentioned discoveries regarding CNS plasticity, on the rehabilitation of patients suffering from CNS trauma due to injury or disease.

As stated in the introduction, various arguments have been raised along the years regarding the existence and

mechanisms of neuroplasticity of the adult mammalian CNS. Barr and Kiernan (1988) claimed that axons in the mammalian brain regenerate successfully only in certain circumstances, and seemed to support the idea that functional recovery is due to the taking over of the functions of the damaged region of the nervous system by other regions that remain intact. Kelly (1985) explained how neurones in the mammalian adult CNS, having withdrawn from the mitotic cycle, are incapable of cell division and thus regeneration following trauma to CNS neurones cannot occur.

But why is it that axons in the adult mammalian CNS fail to regenerate? Is this an inherent feature of the CNS neurones or is it due to a hostile environment? These questions have been among the challenges in neuroscience in the last decade. Schwab (cited in Rennie, 1994) suggested that a major source of inhibition to CNS axonal regrowth comes from oligodendrocytes. He claimed that upon damage to the CNS, they release a factor that stops axons from elongating. Kelly (1985) suggested that proliferation of fibrous astrocytes which act as phagocytes to toxic products of degeneration at the zone of injury, lead to the formation of a glial scar around that zone and block the course taken by regenerating axons thus preventing the reformation of central connections.

In 1981, however, Aguayo & David presented results from studies carried out on rats which revolutionised neuroscience. They suggested that neurones of the CNS have the capacity to regenerate, provided they are in the right biochemical environment. Other experiments to support Aguayo's findings and offer other explanations to the mechanisms via which CNS recovery might occur. These mechanisms will now be discussed.

DENERVATION SUPERSENITIVITY

This phenomenon refers to the compensatory reaction of the receptor site, for example the motor end plate, following neuronal cell death in a motor nerve lesion. The receptor site may increase in numbers or become increasingly susceptible to a neurotransmitter. Denervation supersensitivity was not only observed in skeletal muscle, but also in the dopaminergic cells of the substantia nigra in the basal ganglia in patients suffering from Parkinson's disease (Bishop, 1982d). In this case, this phenomenon caused a lowered threshold of denervated synapses containing dopaminergic receptors, to dopamine. This would produce increased responsiveness to drug replacement therapy because the drug has expanded sites at which to act, where the receptors had extended their territory on the post-synaptic membrane. This phenomenon also has an "economical" value in that

less transmitter substance produces the same action as at a normal synapse.

The mechanism of denervation supersensitivity is still not fully understood, but shows that there is a functional change, apart from the structural one, as seen in the Parkinson's patients' model mentioned above. This phenomenon also challenges the concept that the adult CNS cannot adapt to changes. It shows that the CNS does react following injury, by becoming more sensitive to the neurotransmitter substance, thus allowing conduction to occur at lower thresholds.

COLLATERAL SPROUTING AND SYNAPTIC REMODELLING

From the enormous amount of literature about the mechanisms that account for neuroplasticity, sprouting and synaptic remodelling seem to be supported by the largest amount of experimental evidence (Bach-Y-Rita, 1981; Brodal, 1981). Both phenomena may be considered as positive changes, since they both show that new growth is occurring. It is important to differentiate between the two phenomena. When part of the total input to a neurone is destroyed, surviving fibres replace the lost ones. Reactive synaptogenesis (or synaptic remodelling) occurs in the case of surviving fibres that are neighbours of the lost inputs, and collateral or axonal sprouting occurs when the fibres come from outside the immediate region of the damage. Sprouting is therefore a process of growth from one cell body to another cell in normal growth, a vacancy at a particular site, or a return to a particular site. Collateral sprouts are new axonal processes that have budded off an uninjured axon and grown to a vacated synaptic site. Sprouting has been shown to occur both in the brain (e.g. Raisman, 1969) and in the spinal cord (e.g. Chambers et al., 1977).

Such studies were carried out to investigate whether or not these sprouting fibres establish synaptic contact with the denervated neurones and whether these contacts are functionally active. To obtain functional recovery, the axon needs to reconnect with the appropriate target, but it is still unclear if this occurs.

In investigations on the septal nuclear complex in the forebrain of the adult rat, Raisman (1969) suggested that synaptogenesis in the deafferented septum occurs through synaptic reclaimation, i.e. the reoccupation of vacated postsynaptic sites by collateral sprouts from viable neurones innervating the same target cells in the brain.
Chambers et al. (1977) unilaterally severed cat dorsal spinocerebellar tracts. Clarke's neurones of L3 segment were observed over a period of time and it was noted that synaptic restoration did not occur in all of the neurones of Clarke's nucleus. However, collateral sprouting and formations of new terminals were

evident in some of the atrophic Clarke's neurones. These findings give anatomical evidence for regeneration in the CNS, and as Chambers et al. (1977) suggested, they also provide functional evidence, in that the changes might play a role in neural shock and recovery from it.

Experiments on cats, carried out by Goldberger and Murray (1982), also provided some evidence that sprouting is a major adaptive response in adult CNS plasticity. They partially denervated and observed sprouting in the dorsal roots and dorsal column nuclei of adult cat spinal cords. They suggested that there are certain conditions which are required for sprouting to occur. Thus in their experiment, evidence of lack of an increased neuronal projection in some regions, implying lack of presence of sprouting, was considered to be as important as the presence of increased projections in others. These findings indicate that sprouting is not a universal phenomenon in the damaged CNS.

From this evidence they concluded that sprouting may be limited by a requirement for proximity or overlap, in that it is seen to be a local process, occurring either at the neuronal surface already occupied by the sprouting terminals or in the immediate vicinity. Therefore, it seems that distance is a limiting factor for sprouting. Another condition for sprouting to occur, may be the diversity or specificity of the input of the target region which is determined by the anatomical arrangement of that region within the cord. Finally, the capacity of a particular system to sprout may be modified by a competitive or hierarchical relationship among the remaining pathways, i.e. sprouting of one pathway prevents the formation of persistent sprouts by another (Goldberger & Murray, 1982).

Other researchers suggested that sprouting may have negative consequences. Austin et al. (1958) suggested that sprouting may cause spasticity after spinal cord lesions and Goldberger & Murray (1974) have shown that sprouted anomalous connections in the spinal cord result in exaggerated reflexes after spinal cord lesions. This might show that there is a certain degree of return of function, in that the spinal neurones seem to be regaining excitability. However, there is loss of specificity when neurones are activated by afferents other than those in the normal conditions. The specificity with which connections are re-established and the degree of functional recovery, therefore depend upon the type of change that occurs. Raisman (1969) suggested that the rapid re-occupation of sites by local heterotypic terminals may remove an important stimulus for the regrowth of the severed axons. This may be a factor in the apparent failure of effective regeneration in the CNS. It would seem

from these studies that sprouting may not be helpful to the damaged CNS and may contribute to abnormal functions.

Although no conclusive evidence is available regarding the functional significance of sprouting and synaptic reclaimation, these phenomena imply a degree of structural re-organisation in the lesioned CNS, giving evidence that it is not the unreactive system it was thought to be. However, whether or not sprouting and synaptic reclaimation are helpful to the damaged CNS has yet to be determined.

UNMASKING

Another possible mechanism thought to occur following CNS lesions is the 'unmasking' of previously inactive fibre projections and synapses. It is still unknown whether this mechanism can occur in every part of the CNS and, as with sprouting, it has been suggested that it might have adverse effects (Bach-Y-Rita, 1981). Reflexes that were normal in infancy but had become inhibited during development, e.g. Babinski reflex, and which are considered pathological if they reappear, might become unmasked following the degeneration of these specific inhibitory mechanisms after a CNS lesion (Bach-Y-Rita, 1989). On the other hand, Brodal (1973), reporting about his own recovery process following a cerebro-vascular accident, suggested that it had become very difficult for him to initiate a movement, which in this case might imply that inhibitory processes have become overactive. Therefore, it seems that a lesion in the CNS upsets the balance between inhibition and facilitation, producing this unmasking mechanism.

Dostrovsky et al. (1976) gave an example of the effect of upsetting this excitatory-inhibitory balance. They reported that after partial destruction of the afferent input to the dorsal column nuclei, the innervated zone of the nuclei expanded into the denervated zone within weeks. They assumed that cells that had lost their input following the lesion began to respond to input via intact afferents from other regions previously suppressed by the activity in the main routes. Although this may be a plausible explanation, no direct evidence of the phenomenon was offered.

It is therefore noted that there are controversial ideas regarding this unmasking phenomenon. Experimental evidence from similar studies on rats implied that the cortex works with the "if you don't use it, you loose it" concept (Kidd et al., 1992). This would question the existence of these unused pathways in the brain's reserve capacity, and how they escape disuse atrophy. Therefore, whilst Dostrovsky et al. (1976) supported the existence of this phenomenon, Brodal (1973) seemed to support the assumption that intact fibres "take over" for the damaged ones. These experiments might

therefore show how the lesioned system transfers its information or function onto intact systems which do not normally carry this information. This could imply that in the recovered state, the damaged system could still carry out its original function. Conclusive evidence, however, is still awaited.

DENDRITIC REMODELLING

Although the information for the pattern of dendritic and axonal branching is contained within the cell, experiments have shown that a reduction in the input to a neurone alters its structure. One example was given by Kidd et al (1992) who described studies on the dendritic trees in the motorsensory cortex of rats. The hemisphere contralateral to a preferred paw was seen to have richer and more profusely branched dendritic trees than the other hemisphere. It was shown, however, that following training of the non-preferred paw, the dendritic trees of the non-dominant hemisphere became profusely branched and vice-versa, the dendritic trees in the dominant hemisphere were seen to have shrunk. These findings demonstrated both anatomical and behavioural changes, but did not show which was the primary cause to produce such an effect. The researchers suggested that even in this case, a 'use it or lose it' principle was at work, implying that disuse of the preferred paw caused shrinkage of the dendritic tree on the dominant side and expansion of the dendritic tree on the non-dominant side.

An interesting study, by Carlen et al. (1978), gives evidence of both structural and functional changes in the brains of chronic alcoholics. Eight chronic alcoholics were involved in the study. Six abstained from alcohol and two were non-abstinent. They all received repeated computed tomography scans. Out of the six abstinent alcoholics, four who maintained abstinence and functionally improved, showed partially reversible cerebral atrophy, (via, among other factors, the regrowth of the damaged axonal and dendritic neuropil), and prolonged psychological improvement. These results demonstrated the presence of the phenomenon of dendritic remodelling in the adult CNS. Another study by Sumner and Watson (1971), on the hypoglossal nerves of adult rats in vivo, investigated whether dendrites recovered after contact is restored between the nerve and the originally innervated muscle following nerve regeneration. Their results suggested that dendritic retraction is due to loss of effective neuromuscular contact and that re-expansion of the dendritic field is a direct consequence of re-establishment of such contact. This indicates that dendritic changes may rely on their ability to contact target organs or cells.

These experiments support Brown and Hardman's definition of plasticity (1987), in that they give evidence of an alteration in the local environment causing a change in the dendritic tree phenotype. However, what triggers these morphological changes in the dendritic structure is still unknown.

GRAFTING AND TRANSPLANTATION

Aguayo & David (1981) carried out experiments on adult rats and showed that when peripheral nerve segments were used as 'bridges' between the lower medulla and dorsolateral spinal cord, axons from neurones at both these levels grew approximately 30mm. It seems that when the CNS' glial environment was replaced by that of peripheral nerves, the axons from the neurones in the injured spinal cord and brain stem could elongate for unprecedented distances. This phenomenon implies that the differences in the regenerative capacity of neuronal axons depends more on the environment in which these axons are located, rather than on intrinsic properties of the neurones themselves. Schnell and Schwab (1990) reported evidence of long-distance regeneration of lesioned corticospinal tract fibres in adult rats, after intracerebrally applying neutralising antibodies in implanted antibody-producing tumours. These antibodies acted against myelin membrane proteins which have an inhibitory effect on neurite growth.

The results from such studies are still not sufficient to prove any functional regeneration, but if it is eventually demonstrated that these axons from CNS neurones establish functional connections with cells in the target regions to which they have been directed, it may be possible in the future to apply this technique to bypass damaged CNS tissue and connect the undamaged parts at a distance. This would have extremely positive implications in CNS restoration after injury or disease.

Implantation of embryonic tissue in the form of suspensions or solid grafts in damaged brain regions, has also opened new possibilities for experiments on neuronal reconstruction following brain lesions. In 1981, Bjorklund et al. transplanted embryonic CNS caudate putamen tissue suspension via stereotaxic injection into the dorsal caudate nucleus, in adult rat host brains. It was seen that an abundant fibre outgrowth occurred from the embryonic tissue to the host tissue, thus mediating considerable reinnervation of the previously denervated brain region.

Bjorklund et al. (1980) carried out a study where embryonic substantia nigra was transplanted to the neostriatum in adult rats subjected to a destruction of the nigrostriatal dopamine pathway. These rats showed a characteristic movement disorder due to the lack of the

dopaminergic pathway to the basal ganglia. Results showed that the transplant of embryonic substantia nigra could reinnervate substantial parts of the dopaminergically denervated neostriatum and that this new dopaminergic input could fully compensate for the motor asymmetry that had previously been observed.

The studies mentioned above were all carried out on rats and conclusions derived from the results can only be applied to the human adult CNS with caution. But recently, Gash & Joynt (1987) reported cases of transplants in a number of patients all over the world. So far, only two of these patients appear to have benefited from the procedure and varying degrees of improvement were noted in four other patients. The tissue was implanted, via stereotaxic techniques, in different areas of the brain, thus making close comparison between the cases difficult. The varying results however, give rise to a number of issues, for example, the extent of surgical skill required, disagreement on the optimal site of tissue placement, lack of guarantee regarding the quality of the embryonic cells, and an as yet poorly understood mechanism of the action of the graft. These factors imply that it is still too early to conclude any realistic, positive results from such procedures.

However, application of such techniques raise particular interest in that they may serve as models in the study of human neurodegenerative diseases. For example, they might provide a means of reversing damage to particular neurotransmitter systems in the brain, such as the damage that occurs in Parkinson's disease. Lindvall et al. (1990) reported a case study of a patient severely affected from Parkinson's disease who demonstrated significant improvement in motor performance following transplantation of grafts of foetal dopamine neurones into the putamen. Clinical improvement was correlated with an increased synthesis and storage of dopamine at the site of the implantation, thus indicating that the foetal nerve cells had developed and functioned at the transplant site. This was confirmed by brain scans. It is important to note that this is only a one case study, and it is not reported whether the patient was then followed-up on a long term basis to observe whether or not the transplanted foetal nerve cells survived long term, or if they eventually succumbed to the disease and died in the patient. However, such results are encouraging to further research regarding this procedure.

ROLE OF NERVE GROWTH FACTOR

Nja and Purves (1977) carried out experiments on the superior cervical ganglion of the guinea-pig and suggested that the loss of synapses from sympathetic neurones following axotomy results from a reduction in the amount of nerve growth factor supplied to the ganglion cells.

Other studies reported in Bjorklund & Stenevi (1979) have shown that exogenous nerve growth factor could mimic the action of a yet unidentified endogenous 'trophic' factor which is thought to be important for axonal growth regulation in the CNS. However, the experimental evidence available to support these notions is very limited (Kelly, 1985).

REMYELINATION IN THE CNS

Whilst Schwann cells, responsible for myelin formation in the peripheral nervous system, are capable of regeneration, oligodendroglia, responsible for CNS myelination are incapable of proliferation (Bishop, 1982b). This fact accounts for the irreversibility of demyelinating diseases of the CNS as in multiple sclerosis. Waxman (1982) suggested that various experiments have been carried out in an attempt to promote conduction and remyelination in the CNS, but these experiments were seen to give only transient improvement. Such attempts, though, show that remyelination in the CNS is possible but is still an imperfect process (Bishop, 1982b).

BEHAVIOUR COMPENSATION

Rose (1978) suggested that at the neuronal level, the brain's modified experience is expressed in terms of a modification of biochemistry, of cellular architecture and connectivity. He also claimed that at the behavioural level, plasticity is shown through the capacity of the individual to learn, and to be modified by experience. This implies that learning is only possible because of the brain's plasticity, and that improvement occurring after lesions of the CNS is essentially a learning process: a reaction to a change in its environment.

An example of this phenomenon had been observed in experiments with monkeys carried out by Brinkman et al. (1981), in which cross innervation of muscles of the forearm resulted in gradual adaptation to an imposed disturbance. Following regeneration of the nerves, the monkey could retrieve food using the experimental forearm with good control. This adaptive capacity was described by Craik (1982) as 'function induced plasticity', and its being demonstrated in the monkey (primate), may support the presence of a similar adaptive property also in man.

Adaptive behaviour indicates a capacity of the nervous system to override the basic patterns of certain innate movements under certain circumstances to compensate for unexpected motor behaviour. This might be the underlying principle in certain neurorehabilitative approaches. It must be said, however, that the neural mechanisms underlying such adaptive responses are still being investigated, and this factor might explain why neurorehabilitation does not always succeed in obtaining its goals, as is seen in certain abnormal recovery exhibited by patients who have suffered a cerebrovascular accident or brain trauma.

IMPICATIONS OF CNS PLASTICITY ON NEUROREHABILITATION

The research studies mentioned previously give evidence of the capacity of the nervous system to repair and adapt itself following injury, and do not only serve to explain, at least partially, the mechanisms with which this recovery occurs, but also underline the importance of having a scientific basis for neurorehabilitative techniques in order to be able to improve them (Bach-Y-Rita, 1981). Stephenson (1993) claimed that successful therapy depends on the ability of the CNS to be manipulated and restructured. This indicates that in rehabilitation programmes for adult patients suffering from CNS lesions, plastic changes which enhance normal movement, must be encouraged. Kidd et al. (1992) suggested that this could occur if therapy is able to strengthen normal synaptic chains and neuronal sets, guide axonal sprouting, and facilitate unmasking of alternative or previously unused pathways in the CNS in order to maintain normal function through alternative routes.

Although there is still much controversy about the plasticity of the CNS, Craik (1982) confirmed the above notions and suggested that the assumption of the existence of plasticity in the CNS even following trauma, underlies the majority of treatment approaches used in neurorehabilitation. She, therefore, emphasised the importance of starting neurorehabilitation programmes as early as possible following trauma.

However, more scientific research evidence is needed to bridge the gap between the plastic changes seen to occur in the CNS after lesions and whether or not therapeutic interventions have any influences on those plastic changes.

CONCLUSION

This essay has reviewed a variety of studies which give evidence of some of the possible mechanisms that could underlie the CNS' capacity for repair and regeneration following trauma. The mechanisms reported were mainly denervation supersensitivity, collateral sprouting, unmasking of previously unused pathways, grafting, transplants and implants, synaptic and dendritic remodelling, and other less investigated but significant phenomena such as adaptive behaviour, the role of nerve growth factor in repair and regeneration, and remyelination of diseased CNS axons.

Some practical issues emerge from the results of these studies. For example, the majority of the experiments were carried out on animals and application of the conclusions drawn from the results to the human CNS should be done cautiously. It is understood that studies on humans would imply serious ethical issues because of the difficulty in determining the

extent and location of damage, in obtaining sufficient numbers of patients with similar lesions, in quantifying progress accurately, because of the long recovery time span and the cost involved such long-term rehabilitation programmes.

Another point raised was the fact that structural changes reported, did not always coincide with functional modification. What do the structural changes observed in these experiments mean in terms of human recovery of movement and function? To what degree can the regenerative mechanisms be governed and promoted in favour of greater functional repair after CNS damage? These questions need to be addressed by further research.

The methodology used in carrying out the lesion during the experiments might have affected the results of such experiments. Some methods might have been more sensitive than others. It was also seen that such plastic responses to experimental manipulation could only be evoked over a limited period of time. None of the studies reported long term positive effects. However, these experiments have shown, to varying degrees, that the CNS is certainly not a "once and for all" system and that the previously prevailing view of a fixed and unchanging CNS can definitely be discarded in the light of new evidence.

In the last section of the essay, some implications of CNS plasticity on neurorehabilitation were discussed. It was seen that the concept of a static CNS had delayed the development of theories which could be applied to neurorehabilitation.

Referring back to the introductory statement of this essay, and having reviewed significant evidence in favour of the existence of CNS plasticity, it can be concluded that plasticity modifies the specificity of the CNS. Emphasis should no longer be placed on whether plasticity of the CNS exists or not, but that such evidence should provoke further investigation on how it could be applied to neurorehabilitative treatment approaches in order to promote optimal functional recovery of patients suffering from trauma to the CNS.

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