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Current strategies to repair the injured Central nervous system

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Introduction

Injuries or pathological lesions to the central nervous system (CNS) can have a devastating impact on an individual including physical, emotional and social health [1,2]. The brain and spinal cord, which make up the CNS, are the overall controlling centres for all behaviours and movements [3,4]. For example, spinal cord injury is considered to be one of the major causes leading to a loss of mobility. Damage to the spinal cord often results in permanent disability or loss of movement (paralysis) and sensation below the site of the injury [5]. Lesions within the brain can affect various aspects of behaviour depending on the exact location of the damage. With our current state of knowledge there is little or no prospect of recovery from such injuries or pathological lesions. However, recent scientific advances hold out the possibility that this situation may change in the future with a real prospect of repair of the injured central nervous system. Here we review some of these advances and highlight some of the problems that still need to be solved before such repair is going to become a reality.

The CNS contains billions of neurons which have axons which either interconnect with each other in specific ways or connect, via the peripheral nervous system (PNS) with muscles and other tissues in the body. For example, the spinal cord contains millions of ascending and descending axons which allow communication between the brain and the rest of the body [6]. A lesion to the brain or spinal cord can disrupt some, or all, of this communication network. Often many of the neuronal cell bodies survive the effects of such a lesion but the axons become severed. Much current research is directed towards regenerating these axons after such injuries or lesions and inducing them to locate and re-connect to the correct target tissues.

Injuries to the peripheral nervous system.

It has long been known that axons within mammalian peripheral nerves that have been injured or severed can show some capacity for regeneration and re-myelination. The portion of an axon proximal to a lesion (proximal stump) remains attached to its parent cell body whilst the segment distal to the lesion (distal stump) becomes separated. On occasion, the cell body of an injured axon may die as a result of an injury. Such neurons normally cannot be replaced. Severed axons whose parent cell body have not died as a result of an injury usually degenerate as far back as the first internode. At the same time the cell body begins to up-regulate certain genes, including immediate early genes, in preparation for axon regeneration [7,8]. The distal segment of the axon with its myelin sheath also disintegrates, and the debris is phagocytosed by invading macrophages. Schwann cells, which carry out peripheral axon myelination, proliferate and are thought to up-regulate various neurotrophic factors to prepare the distal segment of the nerve for regenerating axons [9]. These grow from the proximal segment of the nerve and into the neurolemmal bands of Bünger that are left behind after the degeneration of the original axons. These bands of Bünger are thought to both aid the regeneration process and may also be involved in guiding the regenerating axons to their correct target tissues (see the review [10]). Further Schwann cell division takes place and these cells aid in the re-myelination of the newly regenerated axons [8]. This process of degeneration and regeneration of injured axons is termed Wallerian degeneration [11-13]. Research has shown that the presence of Schwann cells is of crucial importance to the process of axonal regeneration [14]. This has been shown in experiments where Schwann cells within segments of peripheral nerve grafts were killed by repeated freezing and thawing procedures. Such nerve segments could not support axonal regeneration until Schwann cells were re-introduced into the grafts [15-17]

Injuries to the mammalian central nervous system (CNS).

In contrast to peripheral nerves, axons in the mammalian CNS only have a limited capacity for regeneration after injury [18]. Lesions in the CNS cause a complex sequence of pathological responses [19,20]. Immediately after injury, there is

extravasation of blood into the lesion site due to the disruption of blood vessels. This results in local ischemia, hypoxemia and hypoglycaemia which help cause secondary damage to the CNS tissue surrounding the lesion site. Several weeks after the injury, microglia and macrophages clear the tissue debris at the lesion site, resulting in cyst formation and cavitation [21-23]. Astrocytes close to the lesion undergo hyperplasia and hypertrophy and are said to become "reactive"[24]. They have been shown to up-regulate molecules such as tenascin, semaphorin 3, slit proteins and chondroitin sulphate proteoglycans [25,26]. These reactive astrocytes contribute to the formation of glial scar tissue [27] that helps to repair the cavities caused by the injury. Axons of injured neurons initially appear to begin to regenerate. However, this regeneration is short lived and stops after they have regrown for a short distance. This failure to regenerate is often termed as "abortive" regeneration [18,28]. The exact reasons for this failure of axonal regeneration are the subject of much research, some of which is reviewed in this paper.

CNS injuries in sub-mammalian species.

A number of sub-mammalian species, including amphibians and some teleost fish (such as zebrafish and goldfish), retain the remarkable ability to repair extensive parts of their CNS after injury [29,30]. This process of repair includes the generation of new neurons (to replace ones that may have been lost), the regeneration and growth of axons to their target sites and the formation of appropriate synaptic connections, thereby restoring lost function [31]. This has led to the establishment of zebrafish (*Danio Rerio*) as an important experimental model in studies on axonal regeneration. A deeper understanding of the factors involved in this regeneration in a sub-mammalian species may give important insights into how we may go about repairing the adult mammalian CNS. It has been found that the zebrafish CNS contains relatively few molecules that inhibit axonal regeneration but has a number of growth factors that may aid such regeneration [32,33]. Zebrafish oligodendrocytes express an array of growth-promoting cell surface molecules of the immunoglobulin super family, as well as a cell adhesion L-1 homolog [34]. It is of interest to note that this is a similar property to that of Schwann cells in the mammalian PNS where axonal regeneration is also known to also occur [9].

Can mammalian CNS neurons regenerate their injured axons?

It was a central dogma held over many years that mammalian CNS neurons were incapable of repairing their injured axons. This was challenged and shown to be untrue by some classical experiments carried out by Ramon-y-Cajal in the 1920's [18] and more recently by Aguyo and his group in the 1980s. Aguyo showed that CNS neurons were capable of extending their axons for up to 35mm into a peripheral nerve graft that bridged a lesion between the medulla and thoracic spinal cord. Whilst the CNS axons regenerated within the peripheral nerve graft their growth ceased once they re-entered into the spinal cord. These experiments clearly showed that mammalian CNS neurons retained their inherent ability to regenerate their axons if they were provided with a suitable environment. Degenerated peripheral nerves provided such a suitable environment but the CNS did not. These experiments led to an explosion of research that was directed to further understanding the factors that either supported or inhibited axonal regeneration within the PNS and CNS respectively [35,36].

Factors that inhibit axonal regeneration in the CNS
Extracellular matrix-associated factors - Chondroitin sulphate proteoglycans (CSPG)

Research has revealed that there are a number of factors present within the CNS that inhibit axonal regeneration. Some of these are related to the astrocytic scar tissue that is formed after injury. This tissue may act both as a physical and chemical barrier to the extension of axons from injured CNS neurons. This scar tissue contains a complex mixture of reactive astrocytes, and various molecules which can either promote or inhibit the growth of different components of the CNS [37]. Chondroitin sulphate proteoglycans (CSPG), which are released by the reactive astrocytes in the region of the scar tissue, have been shown to inhibit axonal regeneration by interfering with integrin signaling mechanisms [38-40]. Recent research has shown that it may be possible to enhance axonal regeneration in CNS tissues by enzymatic digestion of CSPG with the bacterial enzyme chondroitinase ABC (ChABC). This enzyme acts by partially cleaving the GAG side chains on the CSPGs rendering them less inhibitory than they would otherwise be [38,41,42]. Chondroitinase ABC may also limit the extent of glial scar formation after injury, thereby increasing the capacity for axonal regeneration [43].

Myelin-associated inhibitory factors.

1. Myelin-associated glycoprotein.
One of the major differences between the CNS and PNS is that myelination is carried out by oligodendroglial cells in the former and Schwann cells in the latter [44]. As indicated above, the presence of Schwann cells is crucial for the successful regeneration of axons from injured PNS neurons [9]. Myelin also seems to be highly inhibitory to axonal regeneration in both the CNS and PNS. Bedi and his colleagues [45] showed that fresh peripheral nerve cryo-sections

were not capable of supporting axonal regeneration from dorsal root ganglion (DRG) cells in a tissue culture system. However, peripheral nerves which had been allowed to undergo a period of degeneration were able to support such axonal regeneration. It was hypothesised [45] that the presence of myelin within the "fresh" nerve sections inhibited axonal regeneration. Removal of the myelin during the initial pre-degeneration phase after a nerve lesion created a microenvironment which was supportive of such axonal regeneration. This finding initiated a search for the myelin-associated molecules that may be responsible for this effect. Two independent groups [46,47] showed that myelin associated glycoprotein (MAG) was a potent inhibitory factor within both peripheral nerves and within the CNS. Myelin associated glycoprotein is a trans-membrane protein with five extracellular immunoglobulin domains. It is highly expressed in the CNS but also found in the PNS [48] Research has shown that MAG is in fact a bi-functional molecule. It promotes neurite extension from "young" neurons but strongly inhibits such growth in mature neurons [46,47]. The inhibitory properties of MAG are activated through Nogo-receptors [49-52]

2. Oligodendrocyte myelin glycoprotein (OMgp)

Oligodendrocyte myelin glycoprotein (OMgp) is a glycosylphosphatidylinositol (GPI) linked protein which is expressed by both neurons and oligodendrocytes in the CNS. Initially it was thought that OMgp was highly localised in compact myelin. However, it has now been shown [53] that it is particularly localised in the peri-nodal regions of myelinated axons. Although the precise functions of OMgp are yet to be elucidated, it is known that it causes the collapse of growth cones thereby inhibiting axon regrowth. It is also thought to act through the Nogo receptor system [54,55].

3. Nogo-A

Nogo-A is a component of CNS myelin that has been found to restrict regeneration of axons in adult vertebrates [56,57]. It has a 66 amino acid loop structure located between two hydrophobic trans-membrane domains [58]. This component is known as Nogo-66 [50,59] and is involved in causing the collapse of growth cones. The N-terminal domain region of Nogo-A has been shown to also inhibit neurite growth [60-62]

There is much current research directed towards the blocking of the inhibitory properties of Nogo-A as this may offer a therapeutic approach to the treatment of CNS injuries. It has been found that the inhibitory properties of CNS myelin can be partially neutralised by antibodies against Nogo-A and its receptor. Monoclonal antibody, IN-1, is the most frequent antibody used against Nogo-A [63] in experimental studies. Research has demonstrated that injection of IN-1 Fab fragment, directed against Nogo-A specific active sites, into the intact adult rat cerebellum induces sprouting axons and the expression of growth-related genes in Purkinje cells. This suggests that neutralizing Nogo antibodies may induce a growth response in the intact adult CNS [57].

Factors influencing axonal growth and regeneration

Axons grow at specialised regions known as growth cones. These have a number of finger-like projections called filopodia which are thought to "scan" the environment in which they are growing. This allows the axons to respond to the external cues causing them to either grow towards, or be repelled from, a particular direction. There are various axonal guidance molecules such as Ephrins, semaphorins, netrins, slit, cell adhesion molecules (CAMs) and neurotrophic factors that are known to be involved in the control of this process [22,64,65]. The spatio-temporal expression of these factors and their receptors are thought to be involved in the process of CNS development. Repair and regeneration of the injured nervous system may involve the re-activation of some of these developmental mechanisms. Studies using the optic nerves of fish and frogs have indicated that the mature CNS in these species retains the ability to guide regenerating axons to the correct target region [66].Whether or not this can also be achieved in adult mammalian species needs to be elucidated.

1. Cell Adhesion Molecules (CAMs)

CAMs are glyco-proteins that are found on the cell surface and that mediate cell-cell extracellular matrix (ECM) adhesion [18,67,68]. During development CAMs are involved in cell migration, axon guidance, target recognition and synapse formation. In the mature nervous systems CAMs stabilize synaptic connections, cell-cell contacts and neurons-glial interactions [69]. Injuries to the CNS can disrupt these cell-to-cell contacts and lead to death of some neurons. CAMs are therefore thought to be intimately involved in the response of the CNS to injury and may be crucial for the possible regeneration of injured axons [70].

The cell adhesion molecules that are expressed in the CNS can be divided into three classes based on their sequence structures: integrins, cadherins and members of the immunoglobulin superfamily [67,68]. NCAM and L1 are the most relevant to the CNS and may have potential applications in helping axonal regeneration after injury [7a0].

a) L-1 CAM

The L-1 molecule is highly expressed in the developing nervous system and facilitates cell migration, axonal guidance, and fasciculation [71,72] and may also be closely involved myelination [73]. L-1 is thought to provide a suitable substrate for axonal growth and its over-expression has been shown to decrease the amount of specific CSPG which inhibits neurite outgrowth [74].

b) N-CAM

Both neurons and glial cells express N-CAMs which has several isoforms with molecular weights of 180kD, 140kD or120kD [75, 76]. These N-CAMs participate in both homophilic and hetrophilic interactions with neighboring cells [77, 78]. Each NCAM carries a polysialic acid (PSA) carbohydrate moiety which is crucial for NCAM function. PSA is also expressed by reactive astrocytes after CNS injury and this may enhance axonal regeneration [79]. Some studies are now investigating whether cells genetically engineered to over-express PSA can cause the enhancement of axonal regeneration at CNS injury sites. It has been found that axons within the rat corticospinal tracts are able to grow across a lesion site by such treatment [70]. In contrast, treatment of rats with antibodies directed against PSA result in path-finding errors of retinal ganglion cells (RGC) axons during development [79].

2. Axon guidance molecules

There are a number of axonal guidance molecules which are responsible for directing axons to the correct target sites during development. These act by either attracting or repelling axons from growing in a particular direction. With an understanding of the mechanisms of the action of these molecules it may be possible to re-capitulate these events in order to restore the inter-neuronal connectivity after injury or following some therapeutic process [80].

a. Eph and ephrin proteins

The Eph family of tyrosine kinase receptors bind to their membrane-bound ligands, the Ephrins. There are two classes of Ephrins known as Ephrin A and Ephrin B. These bind mainly to Eph-A and Eph-B receptors respectively. Ephrin/Eph signals are important contact-dependent regulators of axonal guidance during development and are responsible for establishing various longitudinal axonal tracts, including the cortico-spinal and retino-tectal systems [81]. The exact mechanisms used to do this are not completely understood but may involve some repulsion and collapse of growth cones due to the eph/ephrin signals [82]. The main mediators of ephrin-induced repulsion are the Rho family of small GTPases, particularly RhoA [83]. RhoA is activated by guanine nucleotide exchange factor, ephenix [84]. The co-expression of ligands during eph/ephrin signalling alters the receptor sensitivity [85]. The extent of this co-expression during development may have a significant role in the establishment of neural pathways in the nervous system [86]. It is thought the eph/ephrin signalling in adults may have a negative impact on axonal regeneration after injury because of its role in the collapse of axonal growth cones [82,87].

b) Semephorins and their receptors

Semaphorins are a family of proteins that share a conserved 500 amino acid motif termed the “sema” domain. There are several classes of semaphorins based on the species in which they are expressed and whether or not they are membrane bound or secreted. They can provide both attractive and repulsive cues to growing axons depending on the exact nature of the semaphorins and receptors involved in any particular location. Semaphorin receptors include plexins and neuropilins. Sema-3 is the class of semaphorins that has been most investigated because of its role in growth cone collapse [88]. It has been found that that semaphorin 3’s and their receptors are expressed in the mammalian spinal cord after injury [82] and it is thought that this is one of the factors that may inhibit axonal regeneration.

c Netrins and Slits

Netrins and Slits are proteins that are expressed near midline structures and control whether or not growing axons are able to cross to the contralateral side of the developing nervous system. Once again, they can act as chemoattractant or chemorepulsive molecules depending on the exact receptors expressed by given axons. Netrins bind to DCC (Deleted in Colorectal Cancer) and the UNC5 family of receptors whilst the Slits bind to Robo (round-a-bout) receptors [82,89]. Once again there is some evidence that netrins and slits are expressed at the site of CNS injury. It is possible that they are therefore inhibitory to axonal regeneration although more extensive research is required to confirm or deny this hypothesis [90].

3. Neurotrophic Factors

Neurotrophins provide trophic support to neurons and promote the growth of axons. They can also act as neuro-tropic factors which help to guide axons to the correct target areas during development of the nervous system [91]. Nerve growth factor (NGF) was the first such factor to be discovered [92,93]. Several others have been described subsequently. These include neurotrophin-3, neuotrophin-4/5, brain-derived nerve growth factor (BDNF), glial cell derived nerve growth factor (GDNF), leukemia inhibitory factors (LIF) and ciliary neurotrophic factor (CNTF) [94,95]. These factors appear to primarily act on given types of neurons or groups of neurons [96]. They have both specific and non-specific

receptors [97]. Once again, the spatio-temporal expression of these neurotrophic factors and their ligands is deeply involved in the successful development of the nervous system. Studies have shown that the regeneration of injured axons is enhanced in the presence of appropriate neurotrophins [98,99]. Establishing the exact combination of neurotrophic factors that may enhance axonal regeneration from given groups of neurons, and the best methods of delivery of these factors to the site of injury, are currently major research objectives. For example, It has been demonstrated that a single injection of NT-3 in combination with IN-1 (a Nogo neutralising antibody) into the rat spinal cord above a site of injury can cause a dramatic increase in the distance that axons are able to regenerate [100]. However, the regenerating axons were still unable to grow across the lesion site in this study.

4. Cyclic adenosine monophosphate (cAMP)

Recent studies have suggested that there is a direct correlation between cellular cAMP levels and the inhibition of neurite outgrowth. Elevation of neuronal cAMP levels following injury can induce axonal regeneration in the CNS [101] and partially overcome the inhibitory effects of CNS myelin [102]. It has been demonstrated [103] that increased levels of cAMP in neurons following injury is mediated by protein kinase A (PKA) inhibitors. The transcription factor, CREB (cAMP response element binding protein] is activated by elevated levels of cAMP [101] and this induces the transcription of proteins which are responsible for axonal regeneration [104].

Other Strategies to repair the injured mammalian CNS

1. Stem Cells

The possible use of stem cells to repair the injured nervous system offers yet another therapeutic approach which has excited researchers and the public at large. Pluripotential stem cells are immature cells that have retained their ability to differentiate into all other cell types in the body. In practise, many so called stem cells are in fact multi-potential rather than pluripotential (i.e. they are able to differentiate into a restricted subset of other cell types found in the body). Neural stem cells have the major characteristics that they can self renew and give rise to many neural cell types, including neurons and glial cells. Neural stem cells have even been isolated from adult CNS tissues and may offer an avenue for the possible replacement of neural cells which have been lost for one reason or another [105,106]. Research is focussing on perfecting methods to isolate and proliferate stem cells so that they can be re-transplanted into individuals as a therapy to treat various brain lesions. Another approach may be to activate endogenous stem cells in situ in order to repair injured brain tissues. Irrespective of which strategy is used to generate the stem cells, it will be necessary to re-integrate the new stem cell-derived neural cells back into the nervous system. New neurons will have to re-grow their axons towards the correct targets and form appropriate synaptic connections in order to restore lost functions. New glial cells will also have to carry out their normal functions. For example, some may have to remyelinate axons that have become demyelinated due to injury or disease processes [107,108]. It is therefore important to have a thorough understanding of the mechanisms that control axonal regeneration and path finding and glial cell functions as these are essential pre-requisites to repair of the injured CNS [109].

2. Olfactory epithelial cell transplants

The olfactory system is one of the few regions in the mammalian CNS where certain neurons are able to regenerate and re-grow their axons to the correct target tissues throughout life. These sensory neurons are located in the nasal epithelium and are particularly susceptible to injury and death due to their continual exposure to an adverse environment. Newly generated neurons are able to grow their axons to the olfactory bulbs and form synaptic connection with the appropriate target cells. Olfactory ensheathing cells (OEC), which are a specialised sub-group of glial cells, aid in this process of axonal regeneration. In experimental studies it has been found that isolated OEC enhanced the extent of axonal regeneration in the injured rat spinal cord and thereby restored some lost functions [110-112]. However, these observations have not always been replicated in other laboratories [113] so further research is required to elucidate the potential use of this strategy to repair the injured CNS before it can be applied to the human situation.

3. Prevention of neuronal cell death

Much human suffering comes about due to the inadvertent or untimely death of neurons in the CNS. This can be as a result of some kind of trauma (e.g. head and spinal cord injuries, ischaemic brain injury), cerebrovascular accident (e.g. stroke) or due to some degenerating diseases (e.g. Parkinson's disease, Multiple Sclerosis, Alzheimer's disease) of the nervous system [114]. Evidence suggests that apoptosis contributes to neuronal cell death in many of these contexts. Understanding the mechanisms of apoptosis has therefore become of vital importance [115]. It has been found that the process of apoptosis is an active rather than a passive cellular process. The cells do not simply die by a failure to

synthesise appropriate proteins. Cells actually die by producing proteins involved in inducing their own death i.e. they 'commit suicide'. This was originally shown by the fact that cells undergoing apoptosis transcribed mRNA, and that this mRNA was translated into certain cell-death associated proteins. It was found that the apoptotic death of cells could be avoided by blocking either the transcription or translation processes involved in the syntheses of these specific proteins [116,117].The genetic control of cell death was first thoroughly investigated in the nematode *C. elegans* [118] In this animal, three genes were found to have a major role in the control of apoptotic death of cells during development. These are ced-9 which was found to promote cell survival and ced-3 and ced-4 which caused cell death. The ced-9, ced-3 and ced-4 genes encode proteins Ced-9, Ced-3 and Ced-4 respectively. These are found to be highly expressed during development of *c. elegans*. The most important finding from the study of the regulation of cell survival in c elegans has been the role of Ced-9 as a "suppressor" of cell death. Ced-9 does not actively promote cell survival but promotes cell survival by suppressing the "death pathways"[119]. It has been found that the ced-9 gene in *C. elegans* exhibits a high degree of homology with the vertebrate bcl-2 gene and there exists a degree of conservation of these two genes across species [120] This conservation is indicative of a common death regulatory pathway consisting of similar active proteins across all species. The bcl-2 gene family has been ascribed various roles of regulating cell survival in vertebrates. The Bcl-2 protein produced by the action of this bcl-2 gene, has been shown to protect cells from a variety of conditions that would normally lead to their cell death. For example, the over-expression of Bcl-2 has been shown to protect sympathetic and sensory neuronal cells from apoptotic cell death in the absence of essential trophic support normally provided by NGF and/or NT3 and/or BDNF [121,122].

Another gene from this family, bcl-x has been found to encode three proteins Bcl-xl, Bcl-xs and Bcl-xβ. It is thought that different tissues can produce different amounts of these proteins by modification of the expression and splicing of bcl-x in order to express proteins best suited to the regulation of cell death within their own circumstances. Bcl-xl is the only protein found in vertebrate neurons where it is constitutively expressed and has also been found to promote cell survival by repressing cell death [117,123]

Bax is yet another protein member expressed by the bcl-2 gene family. It is expressed in many areas of the central and peripheral nervous systems during development. It has been found that both Bcl-2 and Bax can form both homodimers with their own kind and heterodimers with each other. The formation of these hetero and homo-dimers may be involved in the control of the apoptotic pathway by affecting downstream molecules. Homodimers between Bcl-2 promote cell survival whilst those between Bax promote cell death. In contrast, the heterodimers between Bcl-2 and Bax (Blc-2-Bax) promote the steady state position of the cells (Figure 1) [123,124].
It seems the balance between the proteins produced by the bcl-2 gene family play an important role in determining the survival or death of neurons (and other cells) by influencing the downstream "cell death pathways". Proteases

Figure 1

are closely involved in the down-stream cell death pathways [125,126]. It has been known for some time that blocking proteolytic enzymes can rescue injured cells from cell death. More recent research has shown that certain proteases are also involved in the apoptotic cell death pathways. These proteases are known as **C**ysteine requiring **ASP**artate protes**ASE**s, or **CASPASES** [127]. Several caspases have now been shown to be involved in neuronal cell death [128]. Withdrawal of NGF normally leads to death of DRG neurons; it has been found that inhibitors of caspases can rescue such NGF-deprived neurons from such cell death. It has also been shown that Caspase-3 activity is expressed in cell death due to apoptosis but not in necrotic cell death making anti-caspase-3 antibody a very good marker of cells that are in the stages of apoptotic cell death [129,130]. Caspases appear to be a primary agent of cell death in the developing nervous system although other molecules may also be involved in the mechanisms [131].

It is hoped that this research will eventually lead to the development of therapeutic agents to help prevent such cell death during crucial stages of the injury or degenerative processes. Such an outcome could have far reaching effects on the quality of life of people who have been unfortunate enough to suffer such injuries or degenerative diseases. The obvious benefits of this have led to an explosion of research into 'neuroprotection'. This is a term used to describe the effects of various agents or strategies which can be used to intervene in the apoptotic process and thus protect the brain from pathological damage. The agents and strategies that have been, and are being, currently investigated for this purpose are extensive and include pharmaceutic drugs (e.g. alpha-adrenergic agonists and beta-adrenergic antagonists) neurotrophic

factors (e.g. BDNF, CNTF, GDNF), caspase inhibitors (e.g. p35) and various Bcl-2 homologues (e.g. Bcl-X1, antisense oligonucleotides) [27,132,133]. The outcome of this research should eventually lead to better management of the debilitating effects of brain injuries and neurodegenerative diseases**.**

Summary

In summary, the mammalian CNS exhibits very limited capacity for the replacement of neurons that have died or the spontaneous regrowth of axon tracts after injury or pathological process. This inability in mammalian CNS stands in sharp contrast with the situation seen in the CNS of certain sub-mammalian species such as zebrafish.
Our greater understanding of the mechanisms involved in neuronal cell apoptosis opens up the possibility of the development of therapeutic strategies to prevent such cell death. Advances in stem cell technology also offer the possibility of replacing neurons that have died with new neurons that have been differentiated from such stem cells.

Evidence suggests that the failure of successful axonal regeneration in the mammalian CNS is not due to an inherent property of neurons, but mainly due to the environment encountered by regenerating axons [134]. Recent studies have focused on varying the post-lesion microenvironment within the CNS, in an attempt to promote axon growth. These studies have included the use of neurotrophic factors, the blocking of myelin-associated inhibitory molecules and the use of stem cell technology [135]. Although important advances are being made in this research area there are still many mechanisms involved in the process of axonal growth and regeneration to be elucidated. Overcoming the failure of mammalian CNS axons to regenerate after injury remains one the greatest challenges in our quest to repair the injured brain and spinal cord.

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