The Role of Neurogenesis in Neurodegenerative Diseases and its Implications for Therapeutic Development

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Abstract: Neurodegenerative diseases are characterised by a net loss of neurons from specific regions of the central nervous system (CNS). Until recently, research has focused on identifying mechanisms that lead to neurodegeneration, while therapeutic approaches have been primarily targeted to prevent neuronal loss. This has had limited success and marketed pharmaceuticals do not have dramatic benefits. Here we suggest that the future success of therapeutic strategies will depend on consideration and understanding of the role of neurogenesis in the adult CNS. We summarize evidence suggesting that neurogenesis is impaired in neurodegenerative diseases such as Parkinson's, Alzheimer's and Amyotrophic Lateral Sclerosis, while it is enhanced in stroke. We review studies where stimulation of neurogenesis is associated with restored function in animal models of these diseases, suggesting that neurogenesis is functionally important. We show that many current therapeutics, developed to block degeneration or to provide symptomatic relief, serendipitously stimulate neurogenesis or, at least, do not interfere with it. Importantly, many receptors, ion channels and ligand-gated channels implicated in neurodegeneration, such as NMDA, AMPA, GABA and nicotinic acetylcholine receptors, also play an important role in neurogenesis and regeneration. Therefore, new therapeutics targeted to block degeneration by antagonizing these channels may have limited benefit as they may also block regeneration. Our conclusion is that future drug development must consider neurogenesis. It appears unlikely that drugs being developed to treat neurodegenerative diseases will be beneficial if they impair neurogenesis. And, most tantalizing, therapeutic approaches that stimulate neurogenesis might stimulate repair and even recovery from these devastating diseases.

INTRODUCTION

Neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, or Amyotrophic Lateral Sclerosis (ALS), are characterized by a loss of neurons in particular regions of the nervous system. It is believed that this nerve cell loss underlies the subsequent decline in cognitive or motor function that patients experience in these diseases. A range of mutant genes and environmental toxins have been implicated in the cause of neurodegenerative diseases, but the mechanisms remain largely unknown. Nevertheless, current therapeutic strategies have focused on slowing cell loss by antagonizing processes that have been implicated in the degenerative process.

The recent discovery of neurogenesis in the adult nervous system has profound implications for our understanding of brain function and pathology. Neurogenesis refers to the process by which new neurons are generated in the nervous system. The discovery of adult neurogenesis raises the possibility that the nervous system has an intrinsic capacity for repair. Perhaps more controversially, it also raises the question as to whether impaired or failed neurogenesis may contribute to the decline in neurodegenerative diseases. Certainly evidence suggests that neurogenesis is impaired in neurodegenerative diseases such as Parkinson's, Alzheimer's and ALS [1-4]. And, because neurogenesis is enhanced following stroke [5-7], the emerging question is whether this may underlie some of the recovery that is observed in patients following a stroke.

This review proposes that the successful development of new therapeutics for neurodegenerative diseases will depend on understanding neurogenesis. Indeed, as we will discuss below, literature data suggests that many of the processes implicated in degeneration are equally important in the regenerative process. Thus, many drugs, designed to block degeneration by antagonizing these processes, potentially also impair neurogenesis, making them unlikely to be successful in the clinical setting. In support of this argument many of the drugs that successfully entered into the clinic have in fact rarely been found to impair neurogenesis and indeed in some cases appear to stimulate neurogenesis. Even more importantly, evidence is now mounting that stimulating neurogenesis by various means can bring about functional recovery in animal models of neurodegenerative diseases. Thus, a key aim of this review is to suggest that drugs that enhance neuroregeneration may offer hope for therapy in neurodegenerative diseases.

To build our case we will first review neurogenesis in general terms, before highlighting the antidepressants as an example of a clinically practised strategy - albeit not by design - to combat a neurological disorder by enhancing neurogenesis. We will then discuss neuroinflammation to demonstrate the emerging link between inflammation, neurogenesis and neurodegenerative diseases, before discussing literature on selected neurodegenerative diseases in more detail. We will describe the therapeutic strategies in use and in scope for these neurodegenerative diseases and summarize their effects on neurogenesis, where this is known. Before finishing the review with a short discussion of the limitations of animal models in neurodegenerative diseases, we will

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highlight the role of selected ion channels in neurodegenerative diseases and neurogenesis, and review their suitability as therapeutic targets.

NEUROGENESIS IN THE ADULT CNS IS A FUNCTIONALLY SIGNIFICANT PROCESS

This review emphasises that the study of neurogenesis in the adult central nervous system (CNS) is important to understand the actions of current therapeutics and for development of future drugs against neurodegenerative diseases. It thus seems appropriate to first discuss neurogenesis in more general terms.

Neurogenesis is the process by which new neurons are formed from populations of neural stem or progenitor cells residing in discrete regions of the CNS [8-14]. Neurogenesis occurs in four main stages. Firstly, the stem or progenitor cells proliferate; secondly, they migrate into areas of the CNS; where thirdly, they differentiate into the specific neuronal cell type. The fourth and final stage during neurogenesis is the integration of these newly formed neuronal cell types into the pre-existing circuitry. All of these processes play an important role in neurogenesis and contribute to the success of regenerating CNS tissue both in normal and disease states.

Adult neural stem/progenitor cells reside in at least three main areas of the brain, in the anterior part of the subventricular zone (SVZ) along the walls of the lateral ventricles [13, 15, 16], in the hippocampus in the subgranular zone (SGZ) of the dentate gyrus and along the posterior periventricular area (pPV), an extension of the SVZ [17-32].

Studies show that neural stem/progenitor cells exhibit proliferative capacity [25, 33-35]. *In vitro* and *in vivo* studies have shown that adult neural stem/progenitor cells differentiate mainly into neurons with a proportion differentiating into glial cells [18, 20, 32, 36]. These newly generated neurons displayed the morphology of typical neurons and expressed the cell surface markers PSA-NCAM, β-III tubulin, MAP2a, MAP2b and NeuN [18, 20, 32, 36]. They also displayed the electrophysiological properties typical of neurons and made synaptic connections to host neurons and vice versa [18, 20, 32, 36].

It was shown *in vitro* and *in vivo* that newly generated neurons derived from the adult hippocampus exhibited functional properties typical for neurons in the hippocampal formation. Song and colleagues in 2002 [30] showed that adult neural stem/progenitor cells differentiated into neurons that firstly, exhibited the correct neuronal polarity with the formation of dendrites and axons; secondly, expressed the mature neuronal markers; thirdly, formed synapses with primary hippocampal neurons in a co-culture system; and lastly, displayed electrophysiological properties indistinguishable from mature neurons [30]. These *in vitro* studies were supported by studies conducted *in vivo* by van Praag and colleagues (2002) [32] and Shors and colleagues (2001) [37]. Furthermore, on a behavioral level, it has been suggested that neurogenesis in the adult CNS may be important in processes such as memory and learning [27, 32, 37-40].

This postulated functional significance of adult neurogenesis for memory and learning, for example, may have direct consequences for the etiology of some neurological disorders. In fact, numerous studies increasingly point to the idea that depression might be a case in point for this hypothesis.

ANTIDEPRESSANTS INFLUENCE NEUROGENESIS

During the past decade, a series of reports indicated that major depression is frequently associated with significant atrophy within the hippocampus, which can persist for several years after remission from depression episodes [41]. In congruence with this observation, both a reduction in hippocampal volume and a decrease in neurogenesis have been reported in subordinate tree shrews subjected to social interaction stress [41-43]. The hypothesis is that depression and declining neurogenesis in the hippocampus formation is causally connected [44].

Antidepressant treatment can increase neural plasticity, promote de-novo adult neurogenesis, block stress-induced decrease of neurogenesis and upregulate the cyclic AMP-CREB cascade with proliferative effects [45]. Ablation of hippocampal neurogenesis renders antidepressants inactive in behavioural paradigms for antidepressant responses and anxiety-like behaviours in mice [46, 47]. However, ablating neurogenesis in mice does not evoke an increase in depression or anxiety like behaviours indicating that adult-born neurons in hippocampal physiology may be involved in antidepressant therapy rather than in the pathogenesis of depression [46-49]. The only study to date in humans did not detect a difference in proliferation of stem cells in the hippocampus of depressed patients compared to normal subjects [49, 50]. The implications of this for understanding the role of neurogenesis in depression is yet to be resolved.

Among the mechanisms by which antidepressants may exert their effects is by increasing cell proliferation in order to reverse or offset the deleterious effects of stress on the brain [51]. It has been shown that long-term antidepressant therapy is needed to increase hippocampal cell proliferation and reverse the stress and depression-induced decreases in neurogenesis and hippocampal volume, respectively [41, 51]. The mechanism through which antidepressant therapy increases hippocampal cell proliferation may be through the upregulation of brain derived neurotrophic factor (BDNF) [51, 52].

Multiple classes of antidepressants have been shown to increase hippocampal neurogenesis such as selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRI), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, lithium, thyroxine, electroconvulsive therapy (ECT) and exercise [53]. One antidepressant therapy that has been used in models of neurodegenerative diseases is fluoxetine. Fluoxetine treatment has been shown to not only reverse learned helplessness but has also been shown to restore normal neurogenesis [53, 54].

In summary, there is increasing evidence that the beneficial action of several commonly used antidepressants does not only depend on their originally described mechanism of action, but is also, at least partially, due to the stimulation of adult neurogenesis. Thus, it is reasonable to assume that altered neurogenesis may be involved in other neurological disorders, and that stimulation of neurogenesis might have beneficial effects in such conditions. We will start to explore this line of thought further by reviewing the emerging link

between neurogenesis and CNS inflammation that is increasingly implicated in the pathology of neurodegenerative diseases.

THE EFFECT OF CNS INFLAMMATION ON NEUROGENESIS AND NEURODEGENERATIVE DISEASES

The CNS has been traditionally thought of as an immune-privileged system [55, 56]. However, it is known that the healthy adult CNS contains a population of cells called microglia. Microglia are inflammatory cells that are ubiquitously distributed throughout the nervous system. Microglia respond to pathological events such as injury or disease by becoming activated, releasing pro-inflammatory mediators and phagocytosing cellular debris, microorganisms or foreign bodies [57, 58].

CNS inflammation has been shown to play a pivotal role in the disease characteristics of Alzheimer's disease [59, 60], Parkinson's disease [61-63], stroke [64-69], and ALS [70-75]. Studies of post-mortem brain tissue from patients as well as animal models of Parkinson's disease [76-85], Alzheimer's disease [86-92] ischemia/stroke [64-69] and ALS [70-75] showed increased number of activated microglia and upregulated expression of pro-inflammatory cytokines compared to control tissue.

Likewise, studies using animal models of these neurodegenerative diseases show that stimulation of inflammation contributed to the pathology in these models following deposition of α-synuclein in a Parkinson's disease model [93] and formation of Aβ plaques and neurofibrillary tangles in Alzheimer's disease models [94-97]. Furthermore, inhibition of harmful inflammatory processes through non-steroidal anti-inflammatory drugs (NSAIDs) or antibodies directed against pro-inflammatory cytokines in animal models of Parkinson's disease [98-103], Alzheimer's disease [96, 97, 104, 105], and ischemia [66, 67] have resulted in attenuation of neuronal loss, delay of onset and progression of disease and in some cases functional recovery.

Recent studies have demonstrated that inflammation in the CNS regulates neurogenesis, making it possible that altered neurogenesis is at least partially responsible for the effects described above [36, 106-109]. Activation of microglia by systemic inflammation [108] and in models of neurological disease and injury, such as Alzheimer's disease [110], Parkinson's disease, ischemia/stroke, epilepsy [106] and cranial radiation therapy [108], have been shown to have an inhibitory effect on the brain's ability for repair.

A particularly important and influential study by Monje and colleagues in 2003 demonstrated that systemic inflammation stimulated by Lipopolysaccharide (LPS) increased microglial activation in the dentate gyrus and decreased the number of newly generated ($BrdU^+/Dcx^+$) neurons as a result of disruption to the microenvironment and the inability of neural stem/progenitor cells to associate with the vasculature [108]. When systemic inflammation was inhibited by the administration of the NSAID indomethacin, the effect was reversed, resulting in increased neurogenesis. The study further confirmed the negative effect of inflammation on neurogenesis *in vitro* using co-culture systems of microglia and neural stem/progenitor cells derived from the adult hippocampus [108]. Furthermore, this study also noted that patients undergoing cranial radiation therapy experienced a decline in cognitive function, which was accompanied by chronic inflammation that was linked to impaired neurogenesis [108]. It was also demonstrated that irradiated hippocampi displayed increased microglial activation and increased infiltration of the brain by peripheral inflammatory cells such as monocytes. Finally, administration of indomethacin following cranial radiation decreased microglial activation correlating with increased neurogenesis [108].

A second study conducted by Ekdahl and colleagues in 2003 also showed that injection of LPS increased microglial activation and inhibited the formation of new neurons [106]. These authors looked at the role of inflammation in a model of status epilepticus (SE) as acute brain insults have been linked with inflammation and contribute to the pathogenesis of disease and the propagation of neuropathological events. The study found that in SE there was a significant increase in microglial activation in the hippocampus, which also correlated with a decline in neurogenesis [106]. In order to confirm these results, Ekdahl and colleagues showed that inhibition of inflammation observed following SE by administration of minocycline reversed the detrimental effects of inflammation resulting in a decline in microglial activation, which correlated with increased neurogenesis in dentate gyrus [106].

It is clear through these studies that neuroinflammation and more specifically microglia play an important role in the regulation of brain repair by mediating stem cell activity and the microenvironment. Understanding the mechanisms that regulate inflammation in the adult injured and intact hippocampus will aid in the development of therapeutics for neurological diseases where it has recently been shown that inflammation plays an important role in the pathology and progression of the disease. Since CNS inflammation has been increasingly implicated in the pathology of neurodegenerative diseases, inflammation provides a potential mechanism by which neurogenesis is suppressed in these diseases. Whilst targeting inflammation is an increasingly important goal for slowing neurodegeneration, it should also be recognised that this same approach is likely to promote neurogenesis by inhibiting inflammatory mechanisms.

ROLE OF NEUROGENESIS IN NEURODEGENERATIVE DISEASE

Recent literature has suggested that in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, ischemia/stroke and amyotrophic lateral sclerosis (ALS), neural stem/progenitor cell proliferation and neuronal differentiation is altered [1-5, 17, 19, 27, 111-114]. In the following section of the review we will outline the evidence that in particular neurogenesis appears to be impaired in Alzheimer's disease, Parkinson's disease and ALS, raising the question as to whether impaired neurogenesis contributes to the disease progression. We also provide evidence that enhanced neurogenesis following an ischemic-induced neural loss may in fact underlie the partial recovery that occurs after the ischemic episode, although it is presumably not upregulated sufficiently to bring about full recovery.

Evidence for Altered Neurogenesis in Parkinson's Disease

Parkinson's disease is a chronic and progressive movement disorder that is characterised by motor impairments

including limb tremors, muscle rigidity, bradykinesia, akinesia and postural instability [115, 116]. The motor symptoms arise as a result of loss of dopaminergic neurons in the substantia nigra and the subsequent loss of the neurotransmitter dopamine [116]. The loss of dopamine neurons appears to follow from mutations in a range of genes [116, 117] or from exposure to certain neurotoxins [118, 119], although how these different factors lead to cell loss is unknown [116, 120].

Neurogenesis in Animal Models of Parkinson's Disease

It has been suggested that the substantia nigra contains a population of neural stem/progenitor cells and exhibits a basal level of neurogenesis [1-4]. In the 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models of Parkinson's disease, lesions of the substantia nigra stimulated proliferation of neural stem/progenitor cells residing in the substantia nigra [2-4] and increased differentiation of these neural stem/progenitor cells into neurons that expressed the dopaminergic marker tyrosine hydroxylase (TH) [1-4]. However the notion that neurogenesis gives rise to new dopamine neurons is controversial. Indeed some studies suggest lesioning to the substantia nigra following 6-OHDA or MPTP administration, decreased the number of proliferating neural stem/progenitor cells in the SVZ correlating with the extent of dopaminergic denervation [121-123]. Other studies in models of Parkinson's disease have suggested that whilst lesioning the substantia nigra resulted in increased neural stem/progenitor cell proliferation, there was no evidence of differentiation of these neural stem/progenitor cells into dopaminergic neurons [88, 121, 123-131]. The neural stem/progenitor cells, instead, adopted glial phenotypes [125-127, 132].

Effects of Stimulating Neurogenesis in Parkinson's Disease Models

Studies have shown that dopaminergic neurogenesis can be stimulated in animal models of Parkinson's disease through treatments with exogenous factors, which stimulate endogenous populations of neural stem/progenitor cells [128, 129, 133]. Differentiation of endogenous neural stem/progenitor cells into neurons in the substantia nigra was also stimulated in Parkinsonian animals that were housed in enriched environments [134]. Steiner and colleagues showed that enriched environments along with physical activity resulted in increased cell proliferation in the substantia nigra of 6-OHDA injected animals. This housing in enriched environments also led to alleviation of Parkinsonian symptoms including rotational behaviour [134].

The conclusions that can be cautiously drawn from these studies are that the protocols which lead to enhanced neurogenesis seem to bring about functionally beneficial effects. This does not prove that enhanced neurogenesis is responsible for these beneficial effects. While much work still needs to be done, the hope is that neurogenesis leading to repair could offer hope for sufferers Parkinson's disease.

Altered Neurogenesis in Alzheimer's Disease

Alzheimer's disease that presents in patients in their late 40s to mid 50s is characterised in the early stages by progressive memory impairment and cognitive decline, altered behaviour and language deficits [135-138]. In later stages, Alzheimer's disease is characterised by global amnesia and the slowing of motor functions, with death typically occurring within 9 years of diagnosis [136, 138]. Alzheimer's disease is pathologically characterised by neurofibrillary tangles consisting of phosphorylated tau and amyloid β (Aβ) protein deposition forming plaques [137-141].

Neurogenesis is Decreased in Humans with Alzheimer's Disease

Analysis of human brain tissue from Alzheimer's disease patients using immunohistochemistry revealed the presence of neural stem/progenitor cells in the SVZ, dentate gyrus and CA1, CA2 and CA3 regions of the hippocampus [112, 142, 143], with the number of neural stem/progenitor cells in the SVZ being significantly decreased compared to control brain tissue [143]. This suggests that in humans, neuronal degeneration following onset of Alzheimer's disease may result in inhibition of neural stem/progenitor cells and may indicate inhibition of neurogenesis.

Analysis of human hippocampal tissue from Alzheimer's disease patients by Boekhoorn and colleagues in 2006 showed there was not only a significant decrease in the number of neurons in the CA1 and CA2 areas but there was also a significant increase in the number of proliferating cells in the entire hippocampus [142]. However, when specific regions were compared between Alzheimer's disease patients and control patient, there appeared to be no significant changes in cell proliferation [142].

Neurogenesis is Altered in Animal Models of Alzheimer's Disease

This observation in human brain tissue from Alzheimer's disease and control patients is supported by a number of studies using animal models of Alzheimer's disease that also showed decreased neural stem/progenitor cell populations and decreased neurogenesis [144-155]. However, some authors have reported increased neurogenesis in animal models of Alzheimer's disease [142, 156-161]. It is not yet possible to resolve the discrepancies between these studies although one possibility is that the extent of neurogenesis depends on the age of the animal studied. The other possibility is that evidence of enhanced neurogenesis does not mean that the neurogenesis is necessarily proceeding normally.

In vitro studies suggest that proliferation of neural stem/progenitor cells is inhibited by Aβ protein, which in Alzheimer's disease accumulates to form the characteristic Aβ plaques that are believed to contribute to the pathology of the disease [148]. It was further suggested that addition of Aβ protein to cultured neural stem/progenitor cells resulted in decreased migration and differentiation of the neural stem/progenitor cells [148]. These results obtained *in vitro* have been supported by studies conducted in animals models where it was observed that neurogenesis is impaired in mice co-expressing mutant forms of amyloid precursor protein and presenilin1 (APP/PS1 mice) [148, 155, 162-165], or where mutant APP and PS1 are expressed separately (PDAPP, Tg2576, APP Tg, PS1-KO mice) [145, 146, 148, 152-154, 156, 166, 167].

APP/PS1 mice developed Aβ plaques at 6 months of age and displayed decreased neural stem/progenitor cell proliferation and decreased differentiation into mature neurons in

the dentate gyrus [151, 155]. It was also shown that overproduction of APP/Aβ exacerbated cell death of newborn neurons as they approached maturity [151, 155]. This indicates that decreased neurogenesis and neural stem/progenitor cell population may be due to the increased deposition of Aβ and the subsequent development of Aβ plaques.

Individual expression of mutant APP and PS1 in the Tg2576, PDAPP, and the APP23 models or the PS1 P117L, PS1 knock out (KO) and PS1 M146V knock in (KI) models, respectively, has also been shown to increase Aβ42 production and Aβ plaques [144-146, 148, 152-154, 166]. In the PDAPP model, there is increased deposition of Aβ plaques as well as decreasing number of proliferating neural stem/progenitor cells in the SGZ and the granule cell layer (GCL) of the dentate gyrus compared to wild-type controls [145]. These results were supported by studies conducted in other APP Tg models including the Tg2576 model [144, 148, 166].

Studies using animal models where mutant PS1 (presenilin1) is expressed, such as the PS1 P117L and PS1 MS146V KI models, also show significant increases in Aβ42 levels, decreased number of neural stem/progenitor cells and decreased differentiation of these neural stem/progenitor cells into neurons in the dentate gyrus when compared to wild type controls [144, 145, 148, 152-154, 166]. These studies together indicate that PS1 plays an important role in the regulation of neurogenesis in models of Alzheimer's disease.

Whilst most studies using animal models of Alzheimer's disease show that mutations of APP and PS1 are linked to the production and accumulation of Aβ42 protein and Aβ plaques, as well as decreased neural stem/progenitor cell populations and differentiation into neurons in the dentate gyrus, some studies also exist that show increased neural stem/progenitor cell number and neurogenesis [142, 156-159, 161]. In a study by Chevallier and colleagues in 2005, mutant PS1 was shown to stimulate proliferation of neural stem/progenitor cells in the SGZ of the dentate gyrus with no significant difference in their rate of survival or differentiation into mature neurons [158]. Another study also observed that loss of functional PS1 led to premature differentiation of neural stem/progenitor cells into neurons but no changes in the neural stem/progenitor cell proliferation and apoptosis [159]. The effect of loss of both PS1 and PS2 in a double knock out model of Alzheimer's disease strengthens the evidence for a role of presenilin molecules in the regulation of adult neural stem/progenitor cell proliferation and neurogenesis. Regional specific loss of PS1 and PS2 was associated with enhanced proliferation in the dentate gyrus with aging along with increased neuronal differentiation and gliosis in the dentate gyrus of double knock out mice when compared to wild type control mice [157].

There is a Positive Correlation Between Neurogenesis and Functional Recovery in Animal Models of Alzheimer's Disease

Following the studies that showed altered neurogenesis in animal models of Alzheimer's disease and in human brain tissue from Alzheimer's disease patients, it has been demonstrated that neurogenic processes are able to be stimulated, leading to the astounding observation that recovery of the neuronal population is associated with the functional recovery of memory and learning [113, 146, 154, 163, 164, 167-169]. This is perhaps the most important and exciting evidence to date that neurogenesis is functionally important in Alzheimer's disease. By inference, this underpins the proposal of this review that drugs or factors that impair neurogenesis are likely to be detrimental to an Alzheimer's disease patient.

Previous studies have detailed the use of growth factors or environmental enrichment to stimulate neurogenesis in models of Alzheimer's disease. A study by Tsai and colleagues in 2007 detailed the administration of growth-colony stimulating factor (G-CSF) to the Tg2576 mouse model of Alzheimer's disease. It was found that the administration of G-CSF resulted in significantly increased cell proliferation in the dentate gyrus and also induced differentiation of these neural stem/progenitor cell populations into mature neurons. Furthermore, the treatment of Alzheimer's disease mice with G-CSF not only increased neurogenesis but also resulted in improvement of cognitive function indicated by decreased latency time in the Morris water maze test for memory and learning [169].

Several studies investigating Alzheimer's disease models have detailed the benefits of environmental enrichment in stimulating neurogenesis and functional recovery of memory and learning [163, 164, 167]. It has been well documented that environmental enrichment significantly stimulates neurogenesis in the normal adult rodent brain and also significantly improves the memory and learning capabilities of the animal [170-174]. It has also been demonstrated that animals with mutant APP or PS1 housed in an enriched environment had reduced levels of Aβ protein and amyloid deposits [163, 164, 167].

Neurogenesis as a Therapeutic Target for Alzheimer's Disease

Stimulating neurogenesis in models of Alzheimer's disease reduces the appearance of the amyloid plaques characteristic of Alzheimer's disease and appears to contribute to functional recovery with improvement of memory and learning capabilities. Therefore, methods of stimulating neurogenesis are promising therapeutic approaches for treating Alzheimer's disease and other neurodegenerative diseases. The effects of current therapies for neurodegenerative disease on levels of neurogenesis must also be considered in light of the evidence that neurogenesis plays an important role in the recovery of function.

Evidence for Neurogenesis in Ischemia/Stroke

Cerebral ischemia occurs when the brain or parts of the brain do not receive enough blood flow to maintain essential neurological function [175, 176]. The loss of blood supply to the brain results in impairment of glutamate transporters leading to accumulation of glutamate and therefore excessive activation of glutamate receptors and excitotoxic neuronal cell death [176]. When this occurs in humans this is referred to as stroke.

Common deficits that are exhibited following ischemic injury include dysphasia, dysarthria, hemianopia, weakness, ataxia, sensory loss and neglect [177]. At the cellular level, pyramidal cells of the CA1 region are especially sensitive to global ischemia and the duration of ischemia has a direct

effect on the progression of CA1 cell death such that shorter duration of ischemia results in slower progression of the neuronal cell death [178].

Neurogenesis in Humans Following Stroke

Analysis of human stroke tissue demonstrated the expression of markers associated with newborn neurons such as Dcx and β-III tubulin as well as markers of mature neurons such as Map2 and NeuN in the ischemic penumbra surrounding the cerebral cortical infarcts [179]. These findings suggest that stroke-induced compensatory neurogenesis may occur in the human brain and contribute to post-ischemic recovery [179].

Neurogenesis is also Stimulated in Animal Models of Ischemia

Focal ischemia induced by middle cerebral artery occlusion in animal models, results in loss of neurons in the pyramidal regions of the hippocampus and the striatum, and alters the normal pattern of adult neurogenesis. It has been shown that ischemia stimulates cell proliferation within the SVZ and SGZ and migration of newly born immature neurons into the areas of damage [27, 180-184].

Further studies conducted in animal models of ischemia have also provided evidence of stimulated neurogenesis in the hippocampus and in the striatum following ischemia [5, 114, 182, 184-198]. Hence, novel therapeutics aimed at further increasing stroke-induced neurogenesis may contribute to enhanced functional recovery and therefore should be considered in drug development.

Middle cerebral artery occlusion in animals induces loss of pyramidal neurons in the CA1 region of the hippocampus. This is concurrent to increased cell proliferation in the SVZ and SGZ of the dentate gyrus observed between 3 and 28 days after the ischemic episode [27, 187, 192, 198]. Furthermore, neural stem/progenitor cells in the SVZ and SGZ migrate towards regions that exhibit neurodegeneration such as the CA3 and CA1 pyramidal regions [27, 182, 185, 195, 197, 198]. *In vitro*, stroke-derived SVZ neural stem/progenitor cells also exhibited faster migration when compared to non-stroke derived SVZ neural stem/progenitor cells [197]. Finally, the neural stem/progenitor cells differentiated into newborn neurons expressing neuronal markers such as calbindin and formed synapses with neighbouring cells 4-6 weeks after ischemia [114, 185, 187, 195, 199].

Positive Correlation Between Neurogenesis and Recovery in Models of Ischemia

A pioneering study conducted by Nakatomi and colleagues in 2002 showed that stimulation of neural stem/progenitor cells into neurons in the hippocampus following ischemia led to functional recovery in rodents [27]. Treatment of ischemic mice with different growth factors including fibroblast growth factor 2 (FGF-2), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) stimulated neurogenesis in the striatum and hippocampus of ischemic mice [27, 200-204]. Nakatomi and colleagues also showed that the newly generated neurons formed functional glutamatergic synaptic connections to neurons in the pre-existing circuitry [27]. The study investigated further and showed that ischemic animals that received growth factor treatment improved in memory and learning tasks. Therefore, endogenous neural stem/progenitor cells have extraordinary regenerative capabilities and are able to form functional neurons to repopulate areas of degeneration and induce functional recovery [27]. Furthermore, treatment of ischemic hippocampi with VEGF resulted in the significant reduction in infarct volume as well as a marked increase in neural stem/progenitor cell proliferation and differentiation into cortical neurons in the SVZ 14-28 days after ischemia [203]. Increased neurogenesis contributed to improved post-ischemic motor function, thus supporting the regenerative potential of endogenous neural stem/progenitor cells in models of neurodegeneration.

Environmental enrichment is also capable of increasing the level of neurogenesis in the hippocampus and striatum of ischemic animals [27, 201, 202, 204-207]. Environmental enrichment stimulates neurogenesis in normal animals resulting in improvement of memory and learning ability [40, 170-173]. Ischemic mice housed in an enriched environment displayed increased neural stem/progenitor cell proliferation in the SVZ and dentate gyrus and increased number of immature neurons, however, there was no affect on lesion size [208, 209].

Therefore neuronal degeneration following ischemia/stroke stimulates endogenous recovery through neural stem/progenitor cell proliferation and differentiation in regions of degeneration thus indicating the potential that the CNS has to induce functional repair. Further stimulation of neurogenesis may therefore be beneficial and further enhance neuronal and functional recovery.

Evidence for Neurogenesis in ALS

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that is associated with loss of upper and lower motor neurons in the cortex, brainstem, and spinal cord [210]. Symptoms typically start in middle life (40-60 years) and progress rapidly to death, due mostly to respiratory failure, within 2-5 years of diagnosis [211]. For approximately 50% of patients, survival is about 30 months from the onset of symptoms, although there are some that survive beyond 10 years [210].

Patients with ALS present with symptoms that are directly related to the death of motor neurons, such as wasting, weakness, spasticity, difficulty in communicating, dyspnoea, chronic hypoventilation, excessive saliva, fasciculations and cramps, persistent secretions, dysphagia, and emotional lability [210]. In addition there are many symptoms that are indirectly related, such as depression, anxiety, insomnia, fatigue, constipation, pain, and discomfort [210]. However there is relative sparing of the muscles controlling eye movement and the urinary sphincters [212].

Neurogenesis in Animal Models of ALS

Many theories on the underlying ALS pathogenesis have been proposed, including oxidative stress, excitotoxicity, mitochondrial dysfunction, defective axonal transport and abnormal protein aggregation. The identification of mutations encoding the Cu/Zn superoxide dismustase 1 (SOD1) gene have led to the discovery that these mutations are the cause of approximately 10-20% of familial ALS and therefore 2% of all cases [213]. SOD1 knockout mice do not develop overt ALS [214], however, transgenic mice that over-

express the mutant forms of the human SOD1 protein develop an adult onset progressive motor neuropathy phenotype [215]. This model is therefore the most widely used animal model in the study of ALS.

There is evidence of a widespread regenerative response in the spinal cord of ALS transgenic mice [216]. Specifically, there was a significant increase in the number of BrdU-positive proliferative cells in the central canal, grey matter and white matter in the cervical, thoracic and lumbar regions of the spinal cord of ALS mice compared to wild type controls [216]. Despite the presence of a regenerative response, it appears to be largely unproductive as convincing evidence of neurogenesis is absent [216]. Therefore, in ALS mice the neurodegenerative process stimulates a regenerative response, which suggests that the adult spinal cord has at least a limited ability for regeneration [216] but it is inadequate to regenerate the spinal cord.

In studies using the nestin promoter driven LacZ reporter transgenic (pNes-Tg) mice and G93A-SOD1 bi-transgenic mice, it was shown that neural stem/progenitor cell proliferation, migration and neurogenesis occurred in the lumbar region of the adult spinal cord in response to motor neuron degeneration [217]. The neural stem/progenitor cells were restricted to the ependymal zone surrounding the central canal with a significant increase in symptomatic bi-transgenic mice compared to presymptomatic bi-transgenic and pNesTg mice [217]. Once the neural stem/progenitor cells left the ependymal zone of the central canal they lost their proliferative capacity but maintained their migratory function [217]. During disease onset and progression, neural stem/progenitor cells in the ependymal zone of the central canal migrated initially toward the dorsal horn direction then to the ventral horn regions where the motor neurons have degenerated [217]. There was also increased de novo neurogenesis from neural stem/progenitor cells during ALS-like disease onset and progression [217]. This was demonstrated through a significant increase in the percentage of mature neurons in bi-transgenic mice compared to nestin reporter mice [217]. Another study conducted by Chi and colleagues in 2007 also showed significant increases in neural stem/progenitor cells in the dorsal horn in the cervical, thoracic and lumbar regions of the spinal cord at disease onset and in progression stages in bi-transgenic mice compared to age matched pNesTg control mice [218].

Despite the absence of substantial evidence of neurogenesis occurring in ALS, the above two studies do show that there is at least the potential for regeneration in animal models of ALS and therefore, future drug development should consider the possibility of harnessing this potential regenerative ability as a therapeutic target.

CURRENT THERAPIES IN NEURODEGENERATIVE DISEASES AND THEIR ROLE IN NEUROGENESIS AND INFLAMMATION

Currently, therapeutic strategies for neurodegenerative diseases including Parkinson's disease, Alzheimer's disease, stroke and ALS are directed at protecting neurons from degeneration and providing symptom relief. As discussed above, neurogenesis and inflammation may play an important role in these conditions. Therefore we will discuss current therapeutic strategies, their known applications and any possible influences on neurogenesis. Because this connection has not previously been comprehensively investigated, the intention of this review, though controversial, is to highlight this possible relationship and its implications for future therapeutic development

Current Therapeutic Strategies for Parkinson's Disease

Current therapeutic strategies for Parkinson's disease are targeted at providing symptomatic relief *via* replenishing dopamine levels, which are lost as a result of the degeneration of nigrostriatal dopaminergic neurons. However, none of these drugs have yet to been shown to halt or retard dopaminergic neuron degeneration [219].

Levodopa (L-DOPA) is currently the gold standard for Parkinson's disease as it is the most effective therapy in treating the symptoms of the disease [220]. However its effectiveness is limited as long term use over 5-10 years is associated with the development of motor complications in up to 80% of patients [115]. As a result, there are a number of possible alternative therapies which can be used as an adjunct to L-DOPA or as a monotherapy.

Evidence for MAO Inhibitors Influencing Neurogenesis in Parkinson's Disease

Monoamine oxidase (MAO) is an enzyme that catalyses the oxidative deamination of biogenic amines in peripheral tissues and the brain. There are two types of monoamine oxidases: MAO-A and MAO-B. MAO-A preferentially deaminates norepinephrine, serotonin and epinephrine while MAO-B preferentially deaminates benzylamine and phenylethylamine. Dopamine is equally catabolized by both forms of MAO [221]. MAO inhibitors such as rasagiline mesylate and selegiline have been used as monotherapies in patients with early Parkinson's disease and as adjunctive therapies in Parkinson's disease patients receiving treatment with L-DOPA [222] by smoothing out L-DOPA related motor fluctuations and prolonging dopamine-induced responses in midbrain dopaminergic neurons [223].

In models of Parkinson's disease, MAO inhibitors exert neuroprotection against the neurotoxins 6-OHDA and particularly MPTP [224]. Specifically in the MPTP model, MAO catalyses the conversion of MPTP to the neurotoxic MPP^+ form and therefore, administration of MAO inhibitors prevents generation of MPP^+ and the subsequent degeneration of dopaminergic neurons [224].

Furthermore, a study by Sagi and colleagues (2007) investigated the possible neurogenic activity of rasagiline in post-MPTP induced nigrostriatal lesioned mice. The study demonstrated that a continuous administration of rasagiline following MPTP lesion, restored the severe reduction in dopaminergic cell count, striatal dopamine content and tyrosine hydroxylase activity [225]. This demonstrates that rasagiline may have therapeutic use in stimulating neurogenesis.

Evidence for Dopamine Agonists Influencing Neurogenesis in Parkinson's Disease

Experimental studies have provided evidence that the activation of dopamine receptors (D1, D2, D3 and D4) is important in mediating the beneficial anti-parkinsonian effects of dopamine agonists [226]. Dopamine agonists exert their therapeutic effect by directly activating dopamine re-

ceptors, bypassing the presynaptic synthesis of dopamine [226]. Some dopamine receptor agonists used in the treatment of Parkinson's disease include bromocriptine, pergolide, ropinirole, pramipexole and cabergoline [226-228]. The dopamine receptor agonists are highly selective for D2 or D3 receptors and improve parkinsonian symptoms such as bradykinesia, rigor and tremor [228, 229].

There is a growing body of evidence that dopamine receptor agonists exert a neuroprotective role [226, 229, 230]. *In vitro* studies have shown that addition of dopamine agonists to neuronal dopaminergic cell lines protects the dopaminergic neurons against cell loss induced by rotenone, MPP^+, dopamine and hydrogen peroxide [230]. The protection of dopaminergic neurons is not only dependent on the actions of the drugs as dopamine receptor agonists but also on their antioxidant capacity in preventing oxidative stress-induced neuronal cell death [229].

The neuroprotective effect of dopamine receptor agonists observed in *in vitro* studies was supported by studies conducted *in vivo*. Administration of dopamine receptor agonists such as pergolide preserved the integrity of nigrostriatal neurons in the ageing rat brain and protected against the reduction of striatal dopamine and its metabolites following the injection of 6-OHDA [123, 229]. In experimental models of Parkinson's disease, it has been found that dopamine receptor agonists reversed the motor and behavioural deficits induced by MPTP [229].

Recently, it was shown that striatal dopaminergic innervations are important for the proliferation of precursors in the SVZ which is reduced in Parkinson's disease [231]. The mechanism by which these dopaminergic innervations regulate proliferation may be through activation of the D2/D3 dopamine receptors [231]. There is some evidence that the D2/D3/D4 dopamine receptors are capable of influencing proliferation and neural stem/progenitor cells [231]. Specifically, it was shown that D2/D3/D4 transmission stimulated subependymal zone proliferation and D2/D3/D4 activation increased proliferation in neurospheres [123].

Two papers published in 2004 [130, 232], indicated that both *in vitro* and *in vivo* dopamine agonists augmented SVZ cell numbers *via* a recruitment of D3 receptors and that this effect reflects enhanced mitogenesis and not decreased apoptosis [233]. Therefore dopamine receptors may provide an exciting potential therapeutic target for both neuroprotection and neurogenesis in the treatment of Parkinson's disease.

Other Therapies in Parkinson's Disease

The anticholinergics, including the tricyclics, have long been believed to be a successful therapy in the early stages of Parkinson's disease due to their ability to correct the imbalance between the dopaminergic and cholinergic pathways in less advanced forms of the disease by reducing the neurotransmission mediated by nigrostriatal acetylcholine [234].

Amantadine, an antiviral, has been found to enhance release of dopamine from presynaptic terminals and also has modest anti-cholinergic properties [220]. There is recent evidence suggesting a role for amantadine as a potential neuroprotective agent through its ability to block NMDA receptors [220]. Presently there is no evidence that shows that amantadine plays a role in neurogenesis and/or inflammation. However, as there is evidence that some anticholinergic drugs used in Alzheimer's disease promote neurogenesis [113], further work needs to be done to determine whether the modest anticholinergic effects of amantadine and the anticholinergics used in Parkinson's disease may also influence neurogenesis.

Catechol O-methyltransferase (COMT) inhibitors, such as tolcapone and entacapone, are used in the treatment of Parkinson's disease due to the fact that, in the presence of carbidopa, a significant quantity of orally administered L-DOPA is metabolised by COMT in the gastrointestinal tract [220]. This results in a measurable reduction in the amount of levodopa that will ultimately enter the brain. Even though there is currently no evidence that COMT inhibitors affect regeneration, it should be kept in mind that there could still be a possibility of these inhibitors influencing neurogenesis.

Future Therapeutic Targets for Parkinson's Disease

There are a number of other drug targets that are being investigated as potential new therapeutic agents to be used in Parkinson's disease. For example, adenosine A2a receptor antagonists have attracted interest as potential symptomatic drugs for Parkinson's disease [235, 236]. The symptomatic effect of A2a receptor antagonists can be explained by blockade of the A2a receptors on the D2 receptor-expressing striatopallidal neurons, which inhibits their release of GABA in the globus pallidus, ultimately leading to enhanced motor function through the so called indirect motor pathway of the basal ganglia [235, 236]. A2a receptor antagonists affect the release of acetylcholine from striatal cholinergic interneurons as well as affecting the release of dopamine from the nigro-striatal tract [235]. It has also been suggested that A2a receptors might possess neuroprotective properties [236].

Some other potential therapeutics for Parkinson's disease include nicotine which has been shown to protect against degeneration in both the 6-OHDA [237] and MPTP [238] models, however nicotine itself seems to have no anti-parkinsonian effects [236]. Serotonergic receptor agonists may also provide neuroprotective effects as well as extending the duration of L-DOPA action while dramatically reducing levodopa-induced dyskinesias [236]. Other interesting candidates are allosteric potentiators of group III metabotropic glutamate receptors, which have been shown to markedly reverse reserpine-induced akinesia [239]. Many of these drug targets are still currently under investigation or undergoing clinical trials. However the results of these studies should be considered with the possibility that effects of these therapies on neurogenesis may have an influence on their outcomes.

Current Therapeutic Strategies for Alzheimer's Disease

Reduced levels of acetylcholine in the brain are believed to be responsible for some of the symptoms of Alzheimer's disease. Therefore cholinesterase inhibitors (ChEI), like tacrine, donepezil, rivastigmine and galantamine, are used as the primary sources of symptomatic treatment for this disorder. However, tacrine is no longer in widespread clinical use because it is associated with an unacceptable degree of hepatotoxicity [240].

It has been suggested that cholinesterase inhibitors may also play a neuroprotective role, because the addition of a

ChEI to cell culture protects the cells against damage induced by oxygen-glucose deprivation and glutamate-mediating cytotoxicity [240]. Cholinesterase inhibitors could conceivably be used to stimulate neurogenesis because cholinergic receptors are expressed on neuronal progenitor cells and are also coupled to cell proliferation [113]. In the study by Jin and colleagues in 2006, tacrine and galantamine were administered at maximally effective concentrations to cortical cultures and it was shown that basal levels of BrdU incorporation was increased by approximately 40% [113]. However the key question of whether these newly produced cells actually become functional neurons still remains to be answered.

Memantine, a non-competitive NMDA antagonist, is another drug used in the treatment of moderate to severe Alzheimer's disease. Memantine allows normal physiological function of the NMDA receptor while blocking its pathological activation and providing neuroprotection [241]. The use of memantine is associated with significant improvements in measures of cognition, function, and behaviour in both Alzheimer's disease and vascular dementia [242]. Memantine was found to increase BrdU labelling in the dentate gyrus and the SVZ, showing promise of the drug in stimulating neurogenesis in Alzheimer's disease [113]. This is however a rather unexpected result given that NMDA receptor antagonists have been found to inhibit neurogenesis. However, memantine has been recently shown to have numerous other actions and its primary role as an NMDA antagonist at therapeutic doses has been drawn into question [243]. We further explore the role of mememtine and NMDA receptor antagonists in neurogenesis later in this review.

Although the two therapeutic strategies discussed above have shown promise in stimulating neurogenesis *in vitro*, more studies need to be conducted in order to investigate this in animal models and humans. In any case, these intriguing examples highlight previously unknown effects on neurogenesis of drugs used clinically. Hence we suggest that failure of some drugs in clinical trials may be due to unpredicted adverse effects on neurogenesis. This concept may need to be at least considered in future therapeutic development.

Potential Future Therapies for Alzheimer's Disease

Tumour Necrosis Factor alpha (TNFα) has been demonstrated to play a major role in CNS neuroinflammation-mediated cell death in Alzheimer's disease, Parkinson's disease and ALS [244]. There is increasing evidence that suggests that microscopic inflammation resulting from the release of inflammatory cytokines, including TNFα by Aβ-activated microglia plays a central role in the neurotoxicity that occurs in Alzheimer's disease [245]. Therapeutic agents that selectively inhibit the biological activity of TNFα have recently become available for human use and include the dimeric fusion protein called etanercept. Etanercept binds specifically to TNF and blocks its interaction with cell-surface TNF receptors [245]. TNFα antagonists such as etanercept may therefore be useful in combating inflammation in Alzheimer's disease and possibly in other neurodegenerative diseases. As noted previously, therapeutics that block inflammation could be predicted to enhance neurogenesis. The extent to which TNFα antagonists promote neurogenesis needs to be investigated.

Several new compounds are now being tested for safety and efficacy in clinical trials. These include strategies to reduce the pathogenicity of Aβ peptides which are widely believed to play a key role in Alzheimer's disease. For example, in a phase II clinical trial, active immunisation with Aβ42 plus adjuvant appeared to reduce amyloid deposits in some brain regions and improved certain cognitive measures. However, the trial was halted because 6% of immunised patients developed meningoencephalitis [246].

There are a number of other drugs and treatment strategies that are currently undergoing clinical trials and preclinical investigations. These therapeutic agents and targets will not be comprehensively reviewed here but include apoE4, Lithium, which inhibit tau phosphorylation, the antioxidant Q10 [247], zinc, NSAIDs, cholesterol lowering agents [248], nicotine, M2 receptor antagonism, the MAO-B inhibitors and ladostigil [249]. Whilst investigating the neuroprotective effects of these future therapies, the possible influence of these drugs on neurogenesis should also be considered.

Current Therapeutic Strategies for ALS

Currently, there are a number of treatment options available for the treatment of ALS, but Riluzole is the only approved disease-modifying drug. However the effects of riluzole are only modest, with the drug having no effect on muscle strength, quality of life, or functional capacity [250] and prolonging survival by approximately only 3 months after 18 months of treatment [210].

There are a number of drugs that are used to specifically target the symptoms of ALS and as such will only be briefly mentioned in this review. These include compounds such as baclofen, dantolene and tizanidine which act as antispasmodics [251], atropine and hyoscine hydrobromide which are used to control sialorrhea and drooling [252], Cox-2 inhibitors [253], and lorazepam for dyspnoea [210] amongst others. Trials of cocktails of therapies – combining agents such as minocycline, riluzole and nimodipine, have given excellent results in the mouse model [254] and may provide an alternative therapy. An interesting question is whether the use of GABA drugs such as baclofen as adjunct therapy may have some detrimental effect on neurogenesis, given the critical role of GABA in this process (as discussed further later in this review).

Future Therapeutic Strategies for ALS

As Riluzole is currently the only approved disease-modifying drug available in the treatment of ALS, much study is being conducted to try to find additional therapies for this devastating disease. There has been much interest in the tetracycline antibiotic minocycline, as this has been the most effective agent in prolonging survival in the rodent mutant SOD1 model [211] when administered pre-symptomatically [250]. Minocycline works independent of its antibacterial actions, reducing microglial activation and modulating apoptosis [250]. Surprisingly this did not translate to patients when tested in the clinical setting [255]. Gene therapy is another treatment that has garnered more interest recently. In SOD1 mice, intraspinal [256] or intramuscular [257] injection of a lentiviral vector that produces RNA interference-mediated silencing of SOD1 reduced SOD1 ex-

pression, causing a delay in disease onset and progression [250]. However, this approach cannot be taken for the majority of sporadic ALS patients and so offers a limited scope of beneficial outcomes. As oxidative stress is one of the key factors claimed to underlie ALS pathology, antioxidant compounds have been considered as potential therapeutics and include examples such as vitamin E, N-acetyl cystein, and catalase. For example, catalase has been shown to delay the onset of the disease and improve survival in SOD1 mice [258]. N-acetyl cystein has also shown benefits in a cell culture model of ALS and in SOD1 transgenic mice, but unfortunately this benefit has not transferred to human clinical trials [259]. Another interesting treatment that may prove beneficial in ALS is erythropoietin, which has been shown to exhibit neurotrophic effects in *in vivo* and *in vitro* studies [259]. Studies completed on cultured neurons show that erythropoietin inhibits dopamine release [260], protects neurons from glutamate excitotoxicity and has also been shown to modulate inflammation [212].

In light of the evidence above that many of the therapies used or tried for treatment of ALS have shown promise in animal studies but failed in the clinical setting, it must be considered that they are having as yet other unknown effects on the neurological system. Further studies of the effects of these drugs in neurogenesis will need to be conducted.

Current Therapeutic Strategies for Stroke

There are a vast number of pharmacological drugs that are used in the treatment of stroke. However the first line of defence are the thrombolytics, such as tissue plasminogen activator (tPA), which is effective at restoring blood flow after an ischemic attack but must be administered within 3 hours of the ischemic episode to be the most effective [176].

Future Therapeutic Strategies for Stroke

As highlighted above, thrombolytic therapy is the only effective available clinical option for immediate post-stroke treatment. Hence there is currently high interest in finding agents capable of protecting neurons from further post-ischemic degeneration. Below are some examples of currently investigated therapeutic options.

Glutamate receptors such as NMDA receptors and AMPA receptors have been implicated in neurodegenerative conditions such as stroke, Alzheimer's disease and Parkinson's disease. Studies that administered glutamate receptor antagonists in animal studies found greatest efficacy when the antagonist was administered prior to ischemia onset. However these results were not replicated in clinical trials [176]. One potential limitation of such drugs is that they may impair regeneration due to the important role of these ion channels in neurogenesis, as reviewed further below.

Studies have found that transplanted neural stem cells genetically modified to secrete nerve growth factor (NGF) were able to ameliorate the death of striatal projection neurons caused by transient focal ischemia in the adult rat [261]. Although the transplanted cells can survive and partly reverse some behavioural deficits, mechanisms underlying the improvement remain unclear and there is little evidence for neuronal replacement [262]. In most cases only a few grafted cells survive and these do not show the phenotype of the dead neurons, which might indicate an influence on neurogenesis

According to McCulloch and Dewar in 2001, mitogen-activated protein kinases are also an attractive target for drug development because of their multiplicity of actions, which influence not only cell survival and apoptosis but also inflammatory mechanisms [263]. There are still further treatments for stroke that have received interest over the years, such as adenosine 3 receptor agonists [264] and acid-sensing ion channel antagonists [176], but these will not be discussed further in this review.

As has been discussed above, current drug development aimed at treating neurodegenerative diseases is directed at developing therapeutics that either protect neurons from degeneration or focus on relieving the symptoms associated with these disorders. Among the vast number of drugs that have been developed, several have shown effects on neurogenesis. In general, most of the drugs that have been successful clinically have not adversely affected neurogenesis, and have in some cases even increased neurogenesis. Thus, future drug development should in our opinion consider stimulation of neurogenesis, or at the very least, focus on developing therapies that do not inadvertently block neurogenesis.

ION CHANNELS AS THERAPEUTIC TARGETS FOR NEURODEGENERATIVE DISEASES

Below we will focus on ion channel targets currently being considered for treating neurodegeneration and demonstrate how these ion channels also play a role in neurogenesis and/or inflammation. For the sake of argument and brevity, we have focused on a few examples to emphasize these points.

NMDA Receptors

NMDA receptors (NMDARs) are hetero-oligomeric ligand-gated cation channels which are comprised of a glycine-binding NR1 subunit along with one or more glutamate-binding NR2 (A-D) subunits and sometimes a glycine-binding NR3 (A or B) subunit [265, 266]. The subunits are differentially expressed both regionally in the brain and temporally during development [267]. Of the three ionotropic glutamate receptor channel classes, NMDARs are generally the most permeable to Ca^{2+}. Excessive activation of the NMDAR leads to increased intracellular Ca^{2+} which contributes to cell injury or death [268], whereas physiological activation is essential for normal central nervous system function [269]. Potential neuroprotective agents that completely block NMDAR activity are therefore likely to have unacceptable clinical side effects [270], which has been one of the main reasons that many NMDA antagonists have failed in clinical trials.

NMDA Receptor Antagonists Offer Neuroprotection in Neurodegenerative Diseases

Initial clinical studies with high affinity NMDAR antagonists revealed adverse side effects due to the loss of physiological function of NMDARs [271-273]. Hence, much work has been done to determine drugs that can inhibit the excitotoxic effects of NMDARs whilst still allowing enough normal function to occur.

The most widely studied lower affinity non-competitive NMDAR antagonist is memantine. Memantine works by blocking and unblocking the NMDAR ion channel with rapid kinetic and high voltage dependency allowing normal physiological function while blocking pathological activation [274]. Therefore memantine blocks NMDARs when there is a sustained release of low glutamate concentrations thereby preventing the influx of calcium which results in neuroprotection [275]. In animal models of neurodegeneration (associated with dementia), treatment with memantine has been shown to protect cholinergic neurons from Aβ-induced neurotoxicity [276]. In addition to work with animal models, some clinical trials with vascular- and Alzheimer's Disease-related dementia have also demonstrated improvement in neurological symptoms with administration of memantine [277, 278].

Memantine has also been found to have antioxidant properties, which may add additional neuroprotective effects as excitotoxicity is associated with oxidative stress [279]. Some other actions of memantine include non-competitive voltage-independent inhibition of 5-HT_3 receptor currents [280] and blocking of nicotinic acetylcholine receptors [281]. In trials of memantine in moderate-to-severe Alzheimer's disease patients both as a monotherapy and as add-on therapy with cholinesterase inhibitors, deterioration in cognitive, function and behavioural status was delayed compared with controls [277, 282]. Given the advanced clinical condition of the study subjects and the short duration of intervention in the trials, it is unclear whether the beneficial effects of memantine were a genuine reflection of a neuroprotective action, or whether a more immediate pharmacological effect might be a more plausible mechanism (although equally valuable from a symptom relief perspective) [283].

NMDAR antagonists have been found to exert a beneficial effect in experimental models of Parkinson's disease [284, 285] by blocking the development of L-DOPA-induced dyskinesias [286, 287]. A novel non-competitive NMDAR antagonist dextromethorphan (DM) was discovered to be neuroprotective due to its low affinity antagonism in various CNS injury models including focal and global ischemia, seizure and traumatic brain injury [288]. The protective actions seem functionally related to inhibitory effects on glutamate-induced neurotoxicity *via* the NMDAR antagonist actions but may also be due to inhibition of neurodegenerative inflammatory responses [288].

Wide ranges of other NMDA antagonists are being developed or considered for neurodegenerative disease. This includes ifenprodil, several second generation ifenprodil analogues, and nitromemantines which are second generation memantine derivatives [289]. Interestingly, preliminary studies have shown that nitromemantines are highly protective *in vitro* and *in vivo* and they seem to be more effective than memantine [289].

A large number of studies encompassing *in vitro*, *in vivo* and clinical analyses have concluded that lithium is neuroprotective against NMDAR-mediated glutamate excitotoxicity after ischemia [290-292]. Modulation of the NMDAR function is unlikely to be the sole mechanism responsible for lithium's neuroprotective effects as it also protects against other forms of apoptotic insults independent of NMDAR activation in cerebellar granule cells and cortical neurons [290].

NMDA Receptors Influence Neurogenesis

NMDARs are known to play a crucial role in the regulation of neuronal development during embryogenesis and have also been found to regulate the rate of neurogenesis and proliferation in the adult dentate gyrus [293]. Thus, excitation of adult hippocampal neural stem/progenitor cells promotes neurogenesis, which can be blocked by NMDAR antagonists [294]. In addition, NR1 and NR2B subunits have been found to be expressed in some proliferating cells in the adult rat SGZ [293, 295]. Neurospheres from neural stem/progenitor cells isolated from adult mice hippocampus expressed NR1, NR2A and NR2B subunits [296]. Additionally, exposure to NMDA induced c-fos and c-jun expression in neurospheres that could be inhibited by administration of NMDAR antagonists [296]. Sustained exposure to NMDA inhibited neurosphere formation and facilitated differentiation [296].

NMDARs are also associated with the control of plastic processes such as neuronal migration and neurite outgrowth. Glutamate promotes neuronal migration through NMDARs [297] and NMDARs also regulate neurite outgrowth in the hippocampus *in vitro* and *in vivo* [298, 299]. After treatment with an NMDAR antagonist, the expression of PSA-NCAM is upregulated in the granule cell layer, indicating increased numbers of proliferating neural stem/progenitor cells [300]. NMDAR antagonists also have an effect on nestin-positive neural progenitors in the SGZ in adult and aged rats [300, 301]

Although the evidence is strong that NMDARs play a role in neurogenesis, *in vivo* studies have generated complex results. A number of studies have found that treatment of adult rats with NMDA decreases the rate of proliferation and the number of newly generated neurons in the SGZ of the dentate gyrus [302, 303]. Furthermore, administration of both competitive and non-competitive NMDAR antagonists have been found to increase neurogenesis and proliferation in hippocampal region in young adult and aged rats [302-304]. In contrast to the above studies, a study by Joo and colleagues in 2007 found that a single systemic injection of NMDA into rats increased the number of proliferating cells in the dentate gyrus and repetitive stimulation with the same dose of NMDA stimulated the acquisition of neuronal phenotype [305].

An interesting study by Tashiro and colleagues in 2006 found that survival of new neurons was competitively regulated by NMDA receptors soon after neuronal birth [306]. This may have implications on the resulting formation of new circuits and may play a critical role in learning and memory [306].

The mechanism by which NMDARs influence adult dentate gyrus neurogenesis is not fully understood. NMDARs may modulate directly the production of granule neurons because they may be present in precursor cells of the SGZ [303] but may also indirectly influence the rate of division of these progenitor cells by acting on mature granule cells or astrocytes [303]. This NMDA-dependent modulation of proliferation may be mediated by the activation of immediate early genes, which may lead to synthesis of proteins in-

volved in the regulation of cell proliferation, commitment and differentiation [296].

Adult hippocampal neural stem/progenitor cells respond to excitatory stimuli (glutamate or depolarisation) with elevations in intracellular Ca^{2+} levels. Increased intracellular Ca^{2+} from prolonged NMDAR activation might inhibit DNA synthesis [307]. This may go someway to explain contradictory findings in that different lengths of exposure to NMDA will have differential effects. Regardless, it is clear that NMDARs have the potential to affect neurogenesis in more than one way and that the level of NMDAR activation and many other variables between studies will have an important impact on their effect. In terms of applying this to future drug development, it seems likely that the effects of NMDAR agonists/antagonists on neurogenesis will have to be determined empirically and that it is likely to be dependent on the dosing regime.

AMPA Receptors

AMPA receptors (AMPARs) mediate the majority of fast excitatory neurotransmission in the adult mammalian CNS and are targets for multiple signalling pathways that regulate the strength of glutamatergic excitatory synapses [308]. AMPARs are tetramers comprised of 4 glutamate receptor subunits: GluR1, GluR2, GluR3 and GluR4 [308]. The subunit composition varies depending on the brain region but at the hippocampal CA3-CA1 synapse, most AMPARs are heteromers comprised of GluR2 plus GluR1 or GluR3 subunits [308]. The majority of AMPARs in the CNS are GluR2-containing and hence calcium impermeable [309]. However, significant calcium-permeable AMPARs are present in neuronal and glial cells of various brain regions and regulation of these, including expression, assembly, trafficking and turnover is crucial in synaptic plasticity, neuronal development and neurological disease [309]. For example, alterations in AMPARs and other ionotropic glutamate receptors have been reported in depression and following antidepressant treatment. The antidepressant fluoxetine alters AMPAR phosphorylation in a manner expected to increase AMPAR signalling [310].

AMPA Potentiators/Ampakines Enhance Excitatory Transmission in the CNS

Ampakines are a structurally diverse family of small molecules that positively modulate AMPARs and therefore enhance fast, excitatory transmission throughout the brain [311]. Ampakines facilitate the formation of long term potentiation and, therefore, are logical candidates for memory enhancing drugs [311]. Ampakines increase production of neurotrophins, which has led to widespread interest in using them to treat neurodegenerative diseases and some psychiatric disorders such as depression [311, 312]. Positive modulation of AMPARs may also be therapeutically effective in the treatment of cognitive deficits [313].

Many ampakines have clear subunit preferences and could therefore act in a regionally selective fashion [311]. Indeed, Ampakine effects are both regionally specific and selective of behavioural demands, thus producing regionally discrete changes in cortical activity [311]. Ampakines have been shown to improve short term, intermediate and long-term retention and have also been shown to improve the neuropathology of diseases such as Parkinson's disease and Ischemia by restoring the dopamine system and reducing cortical damage, respectively [311].

In cultured rat entorhinal/hippocampal slices, it was shown that treatment with the ampakine CX614 markedly and reversibly increased BDNF and NGF mRNA and protein levels in a dose dependent manner [312, 314]. This is particularly interesting because growth factors such as these are implicated in stimulating neurogenesis. Another ampakine CX516 was shown to reduce the extent of synaptic and neuronal degeneration resulting from excitotoxic episodes and was shown to be neuroprotective when infused into slices either before or after the excitotoxic insult [315]. CX516 also elicited neuroprotection in an *in vivo* model of excitotoxicity displaying a reduction in lesion size and preservation of neurons [315].

Several other classes of AMPAR potentiators have been reported in literature including Pyrrolidones (pracetam, aniracetam), Benzothiazides (cyclothiazide), Benzylpiperidines (CX-516 and CX-546) and Biarylpropylsufonides (LY392098, LY404187, LY450108 and LY451395, LY503430). These AMPAR potentiators modulate fast synaptic plasticity and memory processes and alter downstream signalling pathways. For example, treatment of 6-OHDA and MPTP models with LY503430 resulted in reduced neurotoxicity [316]. The implications of AMPAR modulation on neurogenesis are discussed below.

AMPA Receptor Antagonists are Effective in Reducing Cell Death in Neurodegenerative Diseases

Activation of AMPARs is involved in seizure initiation and maintenance and overactivation of AMPARs produces cell death by either necrotic or apoptotic mechanisms [317]. AMPAR antagonists were shown to reduce cell death in pharmacological studies [318-323] and have demonstrated to be effective in reducing neuronal loss after focal ischemia in middle cerebral artery occlusions [317, 324, 325].

In vivo and *in vitro* evidence indicates that motor neurons are particularly vulnerable to AMPAR-mediated excitotoxicity [326]. Direct application of AMPAR agonists resulted in selective motor neurons loss, which could be prevented by AMPAR antagonists [326]. Administration of AMPAR antagonists in models of motor neuron degeneration was shown to prevent AMPA-induced motor neuron loss resulting in the prevention of AMPA-induced paralysis [327]. Administration of NBQX (an AMPAR antagonist) in mouse models of ALS showed significant improvement in the behavioural scores, including hind leg extension reflex, cage rung grasping and gait [328]. AMPAR antagonists appear to protect neurons through a mechanism involving the upregulation and release of BDNF as exposure of cerebellar granule cells to a blocker of AMPAR desensitisation, AMPA plus aniracetam, evoked an accumulation of BDNF in culture medium [329].

Non-competitive AMPAR antagonists are being pursued for various neurological disorders as a neuroprotective agent and are divided into 2 major classes, positive and negative allosteric modulators [330]. For example, in the middle cerebral artery occlusion model of ischemia the administration of non-competitive AMPAR antagonists, including GYKI 52466, GYKI 53405, EGIS-8332 and EGIS-10608, resulted

in the reduction of infarct size in a dose-dependent manner [331]. Meanwhile, competitive AMPAR antagonists reduced injury from physical brain trauma when administered before or after the insult, but mixed AMPAR/Kainate Receptor (KAR) antagonists are more effective in this model of brain injury than AMPAR-selective drugs [317, 325, 332]. Whilst competitive AMPAR antagonists could have important clinical application as a neuroprotective agent in acute neurodegenerative disorders, the use of AMPAR antagonists in humans needs to be carefully evaluated due to the widespread presence of AMPARs in the CNS. To date, only few clinical trials have been reported [317, 333-336]. In fact, competitive AMPAR antagonists may not be the first choice for neuroprotective drugs; due to their kinetics of binding at the receptor, they preferentially suppress the physiologically relevant component of the postsynaptic glutamate response [337]. Non-competitive blockers such as 2,3-benzodiazepines or the novel neuroprotectant BIIR 561 should be better suited for the treatment of stroke. NBQX and CNQX have been investigated with some success in models of global ischemia, CNS trauma and Parkinson's disease although drug effects mediated through KAR involvement are suspected [338-344]. Treatment of gerbils with global ischemia with NBQX resulted in prevention of the loss of pyramidal neurons in the CA1 region of the hippocampus [342]. In another study NBQX was shown to have positive effects in animal models of Parkinson's disease [344].

Another selective, potent and highly water-soluble AMPAR antagonist is YM872, which provided significant neuroprotection in rat models of ischemia with middle cerebral artery occlusion and significantly lessened neurological deficits in these animals [345, 346]. Meanwhile, *in vitro* and *in vivo* data have shown efficacy of Topiramate (TPM) on treating stroke [347]. Administration of TPM post-insult is protective against selective hypoxic-ischemic white matter injury and decreases subsequent neuromotor deficits [348]. TPM was also shown to attenuate AMPAR/KAR-mediated calcium influx, cell death and kainate-evoked currents in developing oligodendrocytes, similar to the AMPAR/KAR antagonist NBQX [348]. The TPM-induced neuroprotection is therefore, potentially involved in increasing survival of pre-oligodendrocytes, decreasing neuronal apoptosis, inhibiting microglial activation and astrogliosis and decreasing seizure activity [349]. There is also evidence that administration of TPM not only provided neuroprotection but also resulted in significant functional improvement [350].

AMPA Receptors Influence Neurogenesis

Several studies have investigated the role of AMPARs on neural stem/progenitor cell proliferation, neurogenesis and synaptic plasticity in the hippocampus [308, 309, 351-357]. For example, it was shown that systemic injections or intrahippocampal injections of MK801 or NBQX given at the time of ischemia completely blocked the birth of cells in the SGZ as well as inhibiting the death of CA1 pyramidal neurons 15 days after the ischemia [358]. Administration of these antagonists also blocked the induction of synaptic proteins including synapsin-1 in newborn cells, which indicates that these antagonists prevent the formation of functional newborn neurons [358]. These results suggest that whilst AMPAR antagonists such as NBQX have neuroprotective effects, they also have negative effects on the brains ability for neurogenesis and repair. This may have implications for the utility of these drugs in neurodegenerative diseases.

Nicotinic Acetylcholine Receptors

There are two types of acetylcholine receptors, namely nicotinic and muscarinic. This review will only deal with nicotinic acetylcholine receptors but it must be noted that muscarinic acetylcholine receptors and acetylcholine may also play an important role in neurodegenerative diseases in relation to neurotoxicity, neuroprotection, neurogenesis and inflammation. Good reviews on this topic are available [220, 249, 359].

The nicotinic acetylcholine receptors (nAChRs) are ligand-gated cation channels that are transiently opened by nicotine as well as acetylcholine [360]. They are composed of five subunits of which nine α subunits (α2- α10) and three β subunits (β2-β4) have been identified [361]. The multiple combinations of nAChR subunits possess distinct pharmacological and physiological properties and are distributed differentially in various areas of the CNS [362]. There is a high concentration of α7 nAChRs in the hippocampus which supports a role for α7 receptors in the modulation of synaptic plasticity and in memory formation [363].

Expression of Nicotinic Acetylcholine Receptors is Decreased in Neurodegenerative Diseases

Post-mortem brain tissue from Parkinson's disease patients shows a loss of nAChRs in dopaminergic regions consistent with the death of dopamine neurons [364, 365]. The α6/β2/β3 nAChRs are selectively lost in rodent and non-human primate MPTP models of Parkinson's disease suggesting that these types of nAChRs may be important for maintaining dopamine function in Parkinson's disease. This is further emphasised by the fact that L-DOPA exposure preferentially rescues this nAChR subtype, which parallels the rescue of the behavioural phenotype [366, 367].

Nicotine and Nicotinic Receptor Agonists can be Protective in Neurodegenerative Diseases

The various subtypes of nAChRs are permeable to sodium and calcium leading to cell membrane depolarization and increase in cytoplasmic calcium levels [368] and the balance between the levels of these ions may explain the differential protective and neurotoxic effects of different doses of nicotine.

Epidemiological studies have identified an interesting negative correlation between smoking and the development of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease which has lead to the notion that nicotine has the ability to act as a neuroprotective agent [368]. Nicotine has been found to protect against neuronal cell death *in vitro* and *in vivo* although the exact mechanisms have yet to be determined. Nicotine is also known to be toxic under some circumstances and hence the balance between neuroprotection and toxicity by nicotine depends on the dose, developmental stage and regimen of administration [368].

In mice with a copy of the Swedish mutation of amyloid precursor protein (APP) chronic oral administration of nicotine has been found to decrease Aβ levels and plaques and increase the level of α7 nAChRs [369, 370]. This result sug-

gests that the α7 nAChRs play an important role in neuroprotection. The neuroprotective effects of nicotine have been characterized *in vitro* and *in vivo* in a number of neurodegeneration models related to excitotoxicity. Nicotine and nicotinic agonists provide protection against glutamate excitotoxicity, toxicity induced by Aβ and various other mechanisms of cell death and injury [368].

Two studies in 2001 on the 6-OHDA rat model found that nicotine administration produced a dose-related neuroprotection against neurodegeneration, in particular the striatal dopamine neuron loss normally associated with 6-OHDA [237, 371]. This protection however, was also dependent on the degree of injury associated with different doses of 6-OHDA [237]. In addition to dose, the frequency of nicotine exposure also influences its effects. Continuous exposure is not as effective in neuroprotection as acute or chronic intermittent exposure. For example, chronic intermittent nicotine can increase levels of FGF-2 [372-375] whereas continuous infusion of nicotine can decrease FGF-2 levels [376].

Nicotine can however be toxic to developing neurons. Cultured neurons from knockout mice lacking α7 nAChR subunit do not show developmental neurotoxicity to nicotine [377]. Furthermore, stimulation of α7 nAChRs can increase markers of apoptosis in developing neurons and adult hippocampal neural progenitor cells (NPCs) [378-380].

In view of the apparently beneficial effects of nicotine, a number of drugs have been developed that are directed to mimic its effects. GTS21 is a partial α7 nAChR agonist which enhances attention, working memory and episodic memory in healthy human and is less toxic than nicotine [381]. *In vitro*, GTS21 can protect neurons against damage induced by amyloid peptides but despite that, GTS21 has not been a good candidate for clinical use due to its non-specificity, higher affinity for the rodent receptor and low affinity for the human receptor, and limited brain penetration [382-386]. Second-generation α7 nAChR agonists have overcome the limitations of GTS21. Some of the second generation agonists are 4OHGTS, SSR180711, MEM 3454, Quinuclides and ABBF [387]. Some of these drugs are currently undergoing clinical trials.

nAChRs can also be activated by a novel class of drugs called allosteric enhancers, which activate the receptors without binding to the ACh site [388, 389]. Some examples are physostigmine and galantamine, which are currently used for symptomatic treatment for schizophrenia and Alzheimer's disease. Some newer selective allosteric enhancers are beginning to emerge such as PNU-120596 and compounds 2087101, 2087133 and 1078733, which have been described to specifically potentiate some subtype combinations of nAChRs [390, 391].

Nicotinic Acetylcholine Receptors Influence Neurogenesis

A study by Mudo and colleagues in 2007 found that acute intermittent exposure to nicotine treatment significantly enhanced NPC proliferation in the SVZ of the adult rat brain but not in the SGZ and pre-treatment with a nAChR antagonist blocked this effect. The nicotine effect on NPC proliferation is mediated by FGF-2 *via* FGFR-1 activation [392]. Furthermore, Opanashuk and colleagues in 2001 found that nicotine treatment of the cerebellar external granular layer (EGL) precursors *in vitro* elicited a concentration-dependent increase in DNA content and synthesis and that pretreatment with an nAChR antagonist attenuated these changes [393]. It was also found that chronic nicotine treatment for 4-7 days promoted EGL cell survival. The study concluded that the activation of nAChRs directly affected the development of primary cerebellar neuroblasts and that the effects were mediated through the α3 subtype.

Some other studies suggest the opposite. For example, a study by Shingo and Kito in 2005 found that nicotine decreased numbers of PSA-NCAM-positive and NeuN-positive cells in the rat hippocampus in a dose-dependent manner [394]. This result was in line with a study by Abrous and colleagues in 2002 which found that nicotine self administration in rats resulted in decreased expression of PSA-NCAM in the dentate gyrus and significant decrease in neurogenesis and increase in cell death at higher doses of nicotine [378]. Another study found that nicotine particularly in higher doses decreased cell proliferation in the dentate gyrus of rats and also impaired spatial learning [395].

It can be concluded from the above studies that much still needs to be learned about the effects of nAChR subtype activation and neurogenesis and therefore caution must be observed when targeting nAChRs therapeutically as there may be adverse effects on neurogenesis. On the other hand, there is possible potential to enhance neurogenesis when targeting these receptors and this may provide a novel avenue of research.

Nicotinic Acetylcholine Receptors Influence Inflammation

α7 nAChRs are not only expressed in neurons but are also expressed in cultured microglial cells [396] where they can modulate the immune response contributing to AD. For example, a study by de Simone and colleagues in 2005 found that rat microglial cells expressed the α7 nAChR which was activated by nicotine dose-dependently reducing LPS-induced release of IL-1β and enhancing the expression of COX-2 and the synthesis of prostaglandin E2 as a product [397].

Nicotine seems to protect against the development of Alzheimer's disease and Parkinson's disease through anti-inflammatory mechanisms [387]. For example, nicotine abrogates the production of TNF in culture of microglia through a mechanism dependent on ERK and p38 MAPK [396, 398]. A more recent study confirmed these earlier results and also found that nicotine pre-treatment significantly decreased the loss of tyrosine hydroxylase-expressing dopaminergic neurons after LPS-stimulated inflammation [399].

As was noted earlier in this review, inflammation not only affects neurodegeneration, but also has an influence on neurogenesis and, therefore, potentially regeneration. Hence α7 nAChRs, which modulate all these processes, may represent a potential therapeutic target for neurodegenerative and behavioural disorders. The reviews by Conejero-Goldberg and colleagues and de Jonge and Ulloa cover nAChRs and inflammation in a more comprehensive manner [387, 400].

GABA Receptors

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS and is used by most inhibitory neurons. Therefore, perturbations in GABAergic inhibi-

tion have the potential to result in seizures. It is thus not surprising that epilepsy is the most common neurological disorder in which the GABA system is targeted for treatment [401].

There are 3 families of GABA receptors: $GABA_A$, $GABA_B$ and $GABA_C$. $GABA_A$ receptors are the most widely distributed and mediate most of the inhibitory synaptic transmission in the brain. Most $GABA_A$ receptors are composed of two α subunits, two β subunits and a single γ subunit. The subunits are divided into classes including: α1-6, β1-4 and γ1-3. Each GABA receptor contains two GABA binding sites and one benzodiazepine binding site [402].

There are Alterations in GABA Receptors in Neurodegenerative Diseases

Investigations of age-related alterations in $GABA_A$ receptor are presently still inconsistent and contradictory. For example, some reports support the notion that GABAergic neurons and receptors appear more resistant to loss in Alzheimer's disease, some reports describe a reduction in GABA binding in Alzheimer's disease, while yet other authors report no change in the expression of GABA receptors in Alzheimer's Disease [403]. This might partially be explained by plasticity in the subunit composition of $GABA_A$ receptors in the hippocampus of Alzheimer's disease patients. Even though $GABA_A$ receptors are preserved in Alzheimer's disease neuropathology indicating an attempt to maintain a balance in inhibitory tone [404], the specific subunit composition is altered. Specifically, there is significant reduction in α5 subunit levels in severe disease [405]. In agreement with the idea that there is a developmentally regulated alteration in subunit composition, Zhao and colleagues found that GABA was protective to mature but toxic to immature rat cortical neurons *in vitro* under hypoxia [406]. This suggests that the effects of GABA on cortical neurons can be affected by the age and maturity of neurons. Hence, therapeutic influences on GABA receptors may have differing effects on neurogenic regions of the brain compared to non neurogenic regions.

GABA Receptor Agonists Impact on Neurodegenerative Disease

Drugs that target the $GABA_A$ receptor have been used clinically for many years. The most familiar ones are barbiturates and benzodiazepines. The benzodiazepines act at an allosteric site on the $GABA_A$ receptor to increase affinity of GABA [407]. The therapeutic success is based on this positive allosteric modulation that facilitates natural release patterns of GABA rather than non-specific receptor activation that might result from exposure to a GABA agonist [407]. Some other known GABA receptor agonists are ethanol, gamma-hydroxybutyrate, the nonbenzodiazepines (zolpidem, zopiclone and zaleplon), methaqualone, baclofen, muscimol, progabide and tiagabine.

A study by Schwartz-Bloom and colleagues in 2000 on the benzodiazepines diazepam (complete agonist) and imidazenil (partial agonist) found that diazepam administrated after transient forebrain ischemia in gerbils protected CA1 pyramidal cells from the toxic effects of the ischemia and that imadazenil was less effective than diazepam with respect to neuroprotection and prevention of DNA fragmentation [408].

Ethanol triggers widespread apoptotic neurodegeneration throughout the developing brain when administered to infant rodents during the period of synaptogenesis, also known as the brain growth spurt period [409, 410]. Olney and colleagues proposed a dual mechanism of ethanol's apoptogenic action: blockade of NMDARs and hyperactivation of $GABA_A$ receptors. One can speculate on the effect of ethanol on adult synaptogenesis of new neurons in light of the effects on developing brains.

Long term intraventricular administration with the GABA agonist muscimol has been found to promote reformation of the striatonigral pathway arising from transplants by rescuing host substantia nigra neurons from death in rats with striatal ischemic lesion [411]. This study suggests that preservation of the host target neurons by GABA potentiation for grafted cells may increase efficacy of cerebral implants in establishment of the host-graft fiber connections possibly leading to functional restoration. Hence, there may be implications on the effect of GABA receptors and stem cell transplant as a therapeutic strategy for neurodegenerative disease. Another study by Farber and colleagues in 2003 found that muscimol injection into different brain regions of rats treated systemically with a neurotoxic dose of the potent NMDAR antagonist MK-801 provided substantial protection in some of the injected areas such as the anterior thalamus, diagonal band of Broca and RSC. Therefore, GABAergic agents prevent the NMDAR hypofunction state in these areas of the brain [412].

Isoflurane, an anesthetic, provides protection against severe forebrain ischemia in rats and it has been hypothesised that the mechanism of action is attributable to interaction with the $GABA_A$ receptor [413]. In hippocampal slices, 2% isoflurane caused a near complete protection against oxygen-glucose deprivation [413]. The administration of the $GABA_A$ receptor antagonist bicuculline reversed the neuroprotection in a dose dependent manner [413]. Another anesthetic, alphaxalone, also potentiates the GABA receptor in a way similar to the anesthetic barbiturates (eg. Pentobarbitone) but at lower concentrations [414].

Some antiepileptic and anticonvulsant drugs have been found to have effects on $GABA_A$ receptors. Antiepileptic drugs targeting GABAergic transmission can exert neuroprotective effects against ischemia by increasing endogenous GABA levels and *via* activation of both $GABA_A$ and $GABA_B$ levels [415].

Valproate is one of the major antiepileptic drugs with efficacy for the treatment of generalised and partial seizures in adults and children. There is evidence that valproate increases GABA synthesis and release and thereby potentiates GABAergic functions in some specific brain regions such as the substantia nigra [332].

Topiramate is an anticonvulsant, which has been shown to enhance the GABA-mediated Cl- influx into cerebellar granule neurons [416]. Baclofen is a $GABA_B$ agonist, which has been used to treat severe spasticity of cerebral and spinal origin and is effective in animal models for many central and peripheral disorders but side-effects and tolerance development has prevented more widespread use [417]. $GABA_B$ antagonists show great therapeutic promise but lack of brain

penetration or some proconvulsive potential have prevented their clinical development [417].

GABA Receptors Influence Neurogenesis

GABA signalling seems to limit the progression of NPCs through the cell cycle because pharmacological inhibition of $GABA_A$ receptors increases DNA synthesis in NPCs in a slice-culture preparation [418]. Thus, GABA could be a negative signal for proliferation to ensure that proper number of new NPCs and their progeny are generated [419].

Newborn granule cells initially receive only GABAergic synapses even in the adult brain [420], and new neurons in the neocortex and striatum have been found to be GABAergic interneurons [421]. Nestin-positive progenitor cells and radial glia-like stem cells express functional $GABA_A$ and glutamate receptors as well as glutamate transporters in adult neurogenesis [422].

Dentate granule cells in the developing and adult hippocampus display a similar afferent connectivity with regard to glutamate and GABA neurotransmitters [423]. Adult born neurons can fire action potentials in response to an excitatory drive, exhibiting a firing behaviour comparable to that of neurons generated during development [423]. Laplagne and colleagues concluded that neurons born in the developing and adult hippocampus may constitute a functionally homogenous neuronal population. In line with this, another study by Wang and colleagues in 2005 found that establishment of GABAergic innervation in adult neurogenesis mimics the pattern described for brain development [422]. A second study by Laplagne and colleagues in 2007 found no significant differences among GABAergic inputs recorded from neurons born in the embryonic, early postnatal and adult mice. But, embryo-born neurons showed a reduced membrane excitability suggesting a lower engagement in network activity [424].

GABA signalling through $GABA_A$ receptors negatively controls embryonic stem cell and peripheral neural crest stem cell proliferation in the boundary-cap stem cell niche resulting in an attenuation of neuronal progenies from this stem cell niche [425]. Activation of GABA receptors leads to hyperpolarization, increased cell volume and accumulation of stem cells in S phase causing rapid decrease in cell population [425]. $GABA_A$ receptors signal through S-phase checkpoint kinases of the phosphatidylinositol-3-OH kinase-related pathway which critically regulates proliferation independently of differentiation, apoptosis and overt damage to DNA [425]. Furthermore, mice with a heterozygous deletion of the γ2 subunit induced selectively in immature neurons of embryonic and adult forebrain resulted in reduced adult hippocampal neurogenesis associated with the heightened behavioural inhibition to naturally aversive situations known to be sensitive to antidepressant treatment [426]. Deficits in GABAergic neurotransmission and reduced neurogenesis are implicated in the etiology of pathological anxiety and diverse mood disorders [426].

GABA is a signal that regulates the speed of neuronal migration during adult SVZ neurogenesis. SVZ neuroblasts also migrate to injury sites after stroke and in degenerative neurological diseases [427]. In slice cultures of embryonic brain, activation of $GABA_C$ and $GABA_B$ receptors promotes radial migration of postmitotic neurons out of the ventricular zone and intermediate zone and activation of $GABA_A$ receptors produces a stop signal once the cells have reached the cortical plate [428]. It is still unknown whether GABA also regulates neuronal migration during adult hippocampal neurogenesis [419] and further studies need to be conducted to determine this.

A study by Ge and colleagues in 2006 found that newborn granule cells in the dentate gyrus of the adult hippocampus are tonically activated by GABA- and glutamate-mediated synaptic inputs [429]. Even though GABA is the major inhibitory transmitter in the adult brain, it exerts an excitatory action on newborn neurons due to their high cytoplasmic Cl^- content [429]. Furthermore, conversion of GABA-induced excitation into inhibition in newborn neurons leads to marked defects in their synapse formation and dendritic development *in vivo* and hence GABA has an essential role in the synaptic integration of newly generated neurons in the adult brain [429]. In line with this study, another study by Tozuka and colleagues in 2005 found that NPCs receive excitatory GABAergic but not glutamatergic inputs and that the GABAergic excitation promotes neuronal differentiation.

A study by Parga and colleagues in 2007 found that GABA receptors can affect differentiation of mesencephalic precursors into dopaminergic neurons *in vitro*. Treatment with the $GABA_A$ receptor antagonist bicuculline let to a significant increase in number of dopamine cells and treatment with the $GABA_B$ receptors antagonist CGP 55845 let to a significant decrease [430]. The differences in generation of dopamine neurons are due to the differentiation of mesencephalic precursors, which appeared to be mediated by the GABA receptors [430].

Allopregnanolone is a neurosteroid metabolite of progesterone and a barbiturate-like GABA modulator. Allopregnanolone has been found to increase cerebellar granule cell neurogenesis *in vitro,* which was prevented by MgCl, nifedipine, pictoroxin or bicuculline, which suggests that allopregnanolone affects cerebellar neurogenesis by increasing calcium influx through voltage-gated calcium channels and activation of GABA receptors [431].

It can be concluded from the above studies that GABA receptors can affect all stages of neurogenesis such as differentiation, migration and synaptic integration. Hence, great care must be taken when designing therapeutic strategies for neurodegenerative diseases that affect the GABAergic system. It is quite conceivable that drugs that target the GABA system may have effects on neurogenesis. This becomes a particularly interesting consideration given that GABA agonists are often given as adjunct therapy in conditions such as spinal cord injury and ALS. The question must be asked as to whether such compounds affect regenerative processes in these disorders. In addition, further understanding of the effect of GABA receptors on neurogenesis may provide an avenue for therapeutic development.

Voltage Gated Calcium Channels

Multiple types of voltage gated calcium channels (VGCCs) exist and are classified into different functional types. The L-type VGCCs trigger excitation-contraction coupling in skeletal muscle, heart and smooth muscle and control hormone or transmitter release from endocrine cells

and some neurons [432]. L-type channels are observed in cell bodies and concentrated at the base of major apical dendrites in hippocampal pyramidal neurons, whereas N-type channels are localised primarily in apical dendrites [433-435]. Influx of Ca^{2+} through N- and P-type channels controls neurotransmitter release and T-type channels are low voltage-gated Ca2+ channels that have been implicated in repetitive firing and pacemaker activity in the heart and neurons [432].

Voltage Gated Calcium Channel Antagonists Offer Neuroprotection in Neurodegenerative Diseases

In the late 1960's, nifedipine, verapamil and diltiazem emerged as a novel group of Ca^{2+} channel antagonists because of their selectivity in blocking VGCCs [432]. From the viewpoint of the glutamate-Ca^{2+}-overload neurotoxicity hypothesis, inhibition of excessive Ca^{2+} influx into neurons is considered to be important for neuroprotection [432]. Despite the logical step of applying Ca^{2+} channel antagonists directly to neuronal tissue there have not really been any compounds which have been effective in clinical trials [432].

The L-type channel blocker nimodipine reduced the extent of ischemic damage in animal models [436] but did not have a beneficial effect in patients when administered 24-48 hours after stroke. It did, however, demonstrate some benefit when administered within 12 hours [437]. Therefore, it can be concluded that inhibitors of L-type channels may be neuroprotective when administered prior to onset of ischemia or early on in its course [438].

Voltage Gated Calcium Channels Influence Neurogenesis

A study by Luo and colleagues in 2005 found that blockade of the L-type channel prevented neurogenesis in the dentate gyrus and SVZ and downregulated inducible nitric oxide synthase (iNOS) expression in the dentate gyrus after cerebral ischemia in mice. It was therefore suggested that Ca^{2+} influx through L-type VGCCs is involved in ischemia-induced neurogenesis by upregulating iNOS [439].

Allopregnalone is a neuroactive progesterone metabolite, which has been found to significantly increase the proliferation of NPCs from rat hippocampus and human neural stem cells from cerebral cortex in a dose dependent manner [440]. Nifedipine blocked this increase in proliferation consistent with the finding that allopregnalone induces a rapid increase in intracellular Ca^{2+} in hippocampal neurons *via* a $GABA_A$ receptor activated L-type calcium channel [440].

Voltage Gated Calcium Channels Influence Inflammation

Voltage-gated calcium channels along with a wide variety of other ion channels are expressed on microglia [441], and their activation leads to increases in intracellular calcium concentrations that are dependent on external Ca^{2+} and can be blocked by nifedipine and verapamil [442].

We can conclude from these studies that although antagonising VGCCs seems to have a neuroprotective effect in ischemia models, neurogenesis may be adversely affected at the same time. Furthermore the failures of many clinical trials may at least be partly attributed to the inhibition of neurogenesis. Therefore, it is important when considering therapeutics aimed at neuroprotection to also consider their possible effects on neurogenesis.

The intention of this review was not to comprehensively cover all ion channels in neurodegenerative diseases. For further information, for example, on Serotonin and the 5-HT receptor, please refer to reviews available in the literature [53, 443, 444].

APPLICABILITY OF ANIMAL MODELS IN HUMAN NEURODEGENERATIVE DISEASES

Throughout this review we have discussed examples of discoveries made in numerous animal models. However, it must be noted that there are limitations in animal models and their applicability to human diseases and treatments. This is highlighted in examples provided throughout this review of novel compounds that showed promise in animal models but have failed in clinical trials. The possible reasons for clinical trial failures are numerous but one of the most important factors is the fundamental difference between species. For example, the mutant SOD1 rodent models for ALS involves overexpression of the human mutant SOD1 gene. This is in contrast to the single gene dose effect in human mutant SOD1-mediated familial ALS and the fact that most ALS in humans is idiopathic, i.e. non genetic [211]. Another example is one of the most commonly used Parkinson's disease models, the 6-OHDA model, which fails to reproduce all the clinical and pathological features of Parkinson's disease and its acute nature differs from the progressive degeneration of the dopaminergic nigral neurons in Parkinson's disease [445, 446]. Another important reason for poor predictability of preclinical models to the clinical setting may lie in the anatomical differences between species. For example, in large rodents, middle cerebral artery occlusion renders the hippocampus ischemic, whereas in humans the superficial branches of the posterior cerebral artery supply the hippocampus. Hence, stroke in humans does not commonly affect the hippocampus [6].

We have highlighted only a few of the many limitations of animal models, for more comprehensive information on the topic please refer to reviews [446-453] as a sample of the extensive literature on this issue.

CONCLUSION

The traditional definition of neurodegenerative diseases is based on the observations of reduced number of nerve cells at autopsy. The classification of these diseases as neurodegenerative has lead to an enormous effort over many years directed to block neurodegeneration. The rationale behind current drug development for the neurodegenerative diseases thus far has been logical and straightforward: to identify mechanisms, channels, and receptors involved in neurodegeneration, and then to design a compound that will block these processes. This method has had some, yet limited, success as outlined in this review.

Recent advances in the last 10 years have led to the controversial yet exciting possibility that neural regeneration may be an important part of the disease process in neurodegeneration and, therefore, an important therapeutic target. The complexity of neurodegenerative diseases has grown with the knowledge that inflammation may also play a major role in these diseases. Consequently, neural regeneration and inflammation must be considered as a therapeutic target.

This may change the approaches to the development of therapeutic agents to combat these devastating diseases. Given the evidence summarized in this review it is quite possible that drugs designed to target neurodegeneration may also inadvertently block neurogenesis. For example, despite their great promise, many NMDA antagonists have clearly failed when tested in the clinical setting [271-273] and it is possible to propose this may have resulted from their detrimental effects on neurogenesis. It is especially interesting that different NMDAR antagonists have different effects on neurogenesis. Without a full understanding of the mechanisms by which NMDARs contribute to neurogenesis, it is however difficult to know which drugs are likely to be detrimental to regeneration.

Equally important is the possibility that blocking inflammation is therapeutic in these disorders. In this review, we have discussed ion channels and have shown evidence that they are important in inflammation. However, the complexity of the role of ion channels in the different processes is just becoming apparent. Consequently, the implications are that future drug development targeting these channels should include consideration of their impact of neurogenesis and inflammation in preclinical studies.

One major challenge that remains is to understand to what extent animal models truly represent the human disease. There are examples where a therapeutic has shown potential benefit in animal models but failed when tested in clinical trials or has demonstrated adverse side effects. For example the harmful effects of the anti-inflammatory minocycline in human motor neuron disease was surprising given its strongly beneficial effects in animal models [211].

In summary, the landscape of drug development has changed dramatically, and basic science and clinical development must be directed at least in part to dissect the processes involved in neurogenesis. At the very least, any potential detrimental effects of a new drug on neurogenesis must be considered during drug development as it could block regeneration. At most, the potential exists that targeting and stimulating neurogenesis could be a hope in the treatment and recovery of these disorders, although this remains to be proven and more studies need to be conducted. The years ahead are going to be very interesting and offer great promise of new therapeutics for these devastating disorders.

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