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Review Article

Can endogenous stem cells be stimulated to repair the degenerating brain?

A. W. Michell, W. Phillips and R. A. Barker

The Challenge

Neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease and Alzheimer's disease are common and disabling, causing great suffering for those affected and their families, and resulting in a very significant financial burden on the state. Unfortunately at present we can only prescribe symptomatic therapy for these diseases given the absence of truly disease modifying treatments. Furthermore, even extremely effective symptomatic treatments, such as levodopa for PD, tend to become less effective over time, together with the development of unwanted side effects such as dyskinesias and motor fluctuations. There is therefore a great need for neuroprotective or neurorestorative treatments that affect disease progression.

Repairing the degenerating brain represents a great challenge, not least because it is increasingly recognised that the pathology found in these disorders is dispersed throughout the nervous system. Thus in PD, although the hallmark pathology is degeneration of dopaminergic neurons in the substantia nigra, there is evidence for diffuse pathology throughout the brain (Braak et al 2002) affecting noradrenergic, serotonergic and cholinergic neurotransmission, and even affecting peripheral autonomic nerves and the gut (Edwards et al 1992). Thus, although an effective treatment could simply target a site of maximal pathology, a curative therapy will need to have a very much more diffuse action.

The role of cell therapies

Cell therapies represent one appealing disease modifying approach to neurodegeneration. Evidence from recent randomised controlled trials suggests that transplantation of human *embryonic mesencephalic cells* to the striatum of patients with PD can be effective in some recipients (those less than 60 years old with relatively mild disease that is levodopa responsive) (Freed et al 2001; Olanow et al 2003), albeit at the cost of inducing dyskinesias in a proportion of cases. The techniques are still being perfected, and these trials must be interpreted in this light. However, the observation that a patient has maintained a clinical remission sustained over several years following unilateral transplantation of embryonic mesencephalic cells (with ^{18}F-dopa and ^{11}C-raclopride PET demonstration of graft function) provides proof-of-principle support for the technique (Piccini et al 1999). Furthermore there is evidence that the grafting of embryonic cells is safe in other diseases such as Huntington's disease (Hauser et al 2002; Rosser et al 2002) although whether it is effective remains unresolved (Bachoud-Levi et al 2000).

So far human cell transplantation trials have almost exclusively implanted tissue harvested from aborted human foetuses. This of course raises both ethical issues and supply problems, and introduces the risk of infection. Furthermore, the samples contain a relatively unknown mixture of neurons and glia, postmitotic cells and (some) stem cells. One appealing alternative to the use of foetal tissue might be to implant *stem cells* grown in sustainable colonies. Evidence from animal studies shows that these cells can migrate to sites of damage and differentiate to an appropriate phenotype to replace lost cells, although at the risk of tumour formation if undifferentiated embryonic stem cells are transplanted (Bjorklund et al 2002). However, despite the promise there are still several hurdles to overcome before stem cell transplantation could be used clinically (Text Box 1, reviewed by Lazic & Barker 2003).

An appealing alternative would be to avoid transplantation, and instead *stimulate the endogenous stem cells* that are now known to reside even in the adult mammalian brain

Department of Neurology, Cambridge Centre for Brain Repair, Forvie Site, Robinson Way, Cambridge, CB2 2PY, UK

A. W. Michell, W. Phillips, R. A. Barker

Correspondence: A. W. Michell, Department of Neurology, Cambridge Centre for Brain Repair, Forvie Site, Robinson Way, Cambridge, CB2 2PY, UK. E-mail: awm13@cam.ac.uk

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Text box 1 Problems with stem cell transplantation for neurodegenerative disease

- **Ethical:** The initial creation of embryonic stem cell lines by nuclear transfer requires use of early post-fertilisation human eggs.
- **Purity 1:** Cell lines propagated in culture require regular verification of their purity and genetic integrity. With the generation of offspring they tend to become increasingly heterogeneous over time.
- **Purity 2:** There are no definitive stem cell markers to select a pure group of cells of a known potency for transplantation. Furthermore, the optimal proportion of neurons to stem cells to supporting cells is not yet known.
- **Purity 3:** Many embryonic stem cell lines are grown on non-human feeder cells, thus posing a risk of cell fusion and infection.
- **Rejection:** The brain, although an immunoprivileged site, can mount an immune response against the implanted cells, especially if a xenograft.
- **Tumour formation:** Transplantation of embryonic stem cells in mice has tended to result in teratoma formation if cells are not predifferentiated.
- **Focal**: Most neurodegenerative diseases affect the brain diffusely, yet cells can only be transplanted to focal regions of the brain.
- **Surgical complications:** Any transplantation therapy involves the risk of bleeding and infection inherent to any surgical treatment.
- **Efficacy**: Even if all the above problems can be overcome we have no idea whether implanted stem cells could survive, migrate, differentiate and integrate with the diseased brain in sufficient numbers to provide clinical improvement.

(including human) to repair the damaged CNS. It is this latter area that we will explore in this review. To do this we will first discuss where stem cells are normally found in the adult brain, and whether they can be stimulated to proliferate and differentiate as well as respond appropriately to brain injury. We will then consider whether the diseased state affects these cells, and ask whether the endogenous stem cell remains responsive to stimulation in this situation.

What is a stem cell?

A stem cell can be simply defined as a cell that undergoes prolonged self-renewal and can produce more than one type of highly differentiated descendent (Figure 1). Shortly after fertilization there are cells within the inner cell mass of the pre-implantation blastocyst that are *pluripotent*, that is they can give rise to cells from all three germ layers: endoderm, mesoderm and ectoderm (they cannot, however, produce placental trophoblasts and are therefore not considered '*totipotent*'). These are termed embryonic stem (ES) cells. Primordial germ cells are also pluripotent, and can either be obtained from the embryonic gonad (embryonic germ cells) or from adult gonadal teratocarcinomas (embryonal carcinoma cells).

Distinct from these cells are *multipotent* stem cells that arise later in development and are somewhat more restricted in the cellular phenotypes they can create. Until recently it was felt that these stem cells were lineage restricted to certain tissues, with neural stem cells producing neurons and glia, haematopoietic stem cells producing blood cells and so on. This view is now being challenged, with evidence for transdifferentiation – the ability of a seemingly lineage-restricted stem cell to produce progeny of a different tissue type. For example there is evidence that bone marrow stromal cells might be able to replace lost neurons, even if injected peripherally (Chopp & Li 2002; reviewed by Priller 2003). Finally, *precursor cells* and transit amplifying cells retain the capacity to proliferate (although not necessarily indefinitely), but produce usually a single cell type and are therefore not true stem cells.

Where are stem cells found in the brain?

The answer to this question depends on whether we consider only areas of constitutive neurogenesis under normal conditions, or whether we include regions where stem cells might lie dormant but responsive to stimulation. Furthermore, it depends whether cells are studied in-vivo, or grown in-vitro. It is now generally accepted that there are two main regions of ongoing neurogenesis in many (but not all – see below) adult mammals (for a review see Seaberg & van der Kooy 2002 and Arlotta et al 2003). The subventricular zone (SVZ) around the lateral ventricles generates cells that migrate via the rostral migratory stream towards the olfactory bulb where they differentiate to neurons. On the other hand the subgranular layer of the dentate gyrus (DG) of the hippocampus contains neural precursors that generate new neurons destined for the granular layer of the hippocampus (Figure 2).

The identity of the stem cells within these two main neurogenic regions has recently been reviewed elsewhere (Doetsch 2003; Horner & Palmer 2003). They are defined as astrocytes on the basis of their glial fibrillary acidic protein (GFAP) expression and a characteristic ultrastructure comprising glycogen granules, thick bundles of intermediate filaments and gap junctions. It is important to remember of course that there are many types of astrocyte, not all of which have stem-like properties. Those astrocytes that act as stem cells represent an adult equivalent of the neuroepithelial stem cell active during embryogenesis, or the radial glia seen in early development, but they seem to be less potent. For example, reptiles and amphibians maintain radial glia into adulthood and have a marked capacity for brain regeneration that is unparalleled in adult mammals in which the radial glia are lost.

Since it is desirable to be able to manipulate endogenous neural stem cells to repair the diffusely damaged nervous system it is clearly important to determine whether they exist in-vivo outside these two regions. Constitutive cortical neurogenesis has been reported by one group (Gould et al 1999), but their findings have not been replicated and are still debated (Rakic 2002).

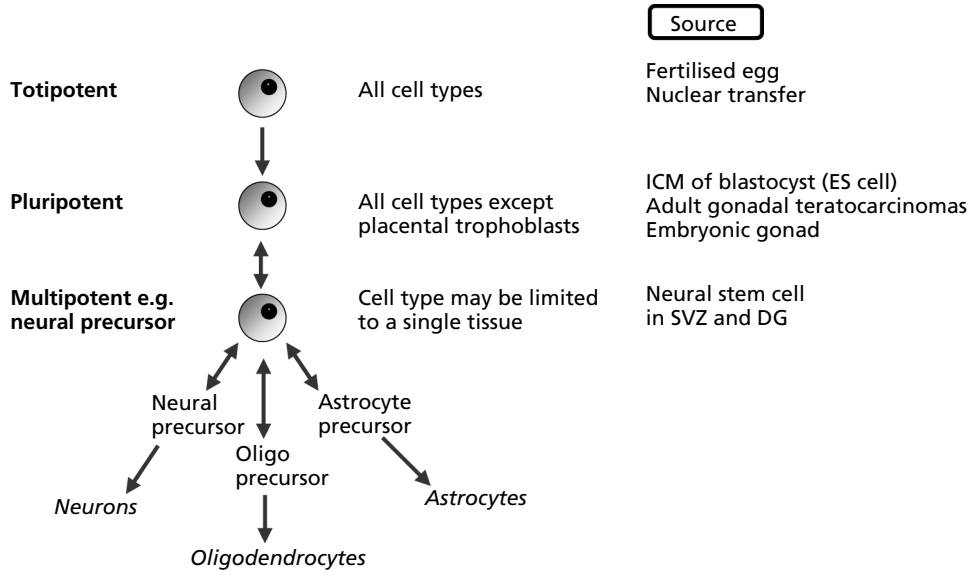

Figure 1 The different potency of stem cells. Note the diagram is simplified for clarity. There is evidence to suggest that some cells can regain their potency (reversal of arrows) before undergoing terminal differentiation to neurons or glia. Furthermore, a separate glial and neuronal precursor may well exist but has not been shown. The term precursor is often used to describe a cell with limited potency and longevity such that it is felt not to meet the definition of a true stem cell. ICM, inner cell mass; ES, embryonic stem cell; SVZ, subventricular zone around the lateral ventricles; DG, dentate gyrus of the hippocampus.

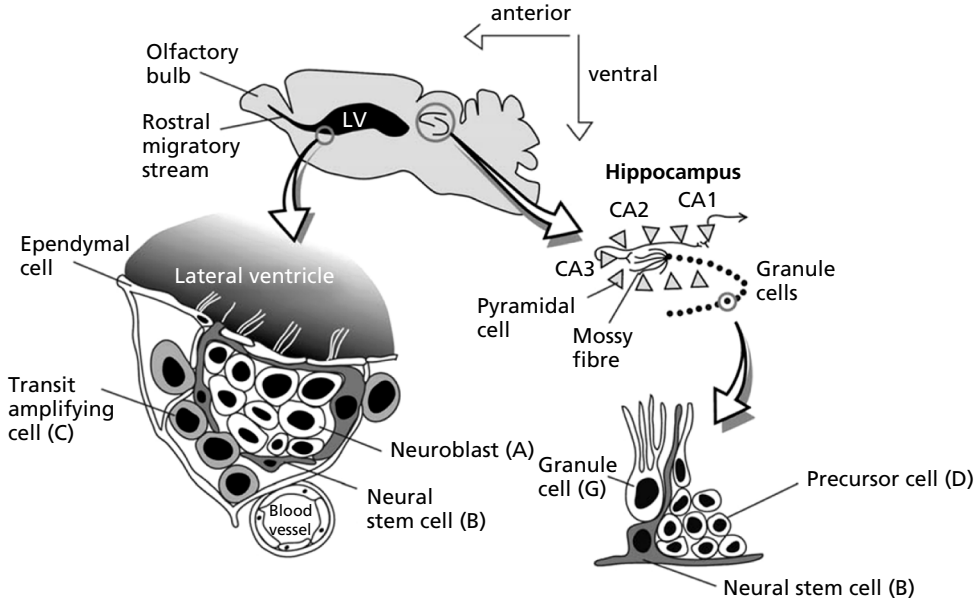

Figure 2 The site of neural stem cells in the adult mouse brain. The subventricular zone lines the lateral ventricles, where type B cells (stem cells) generate type C cells (transit amplifying) and then type A cells (the migrating neuroblasts). In the subgranular zone of the hippocampus, the neural stem cell generates precursors with a dark appearance (D cells), which subsequently divide to produce granule cell neurons (G). LV, lateral ventricle (after Doetsch et al 1999).

Furthermore, ongoing neurogenesis has been reported in the substantia nigra of mice (Zhao et al 2003), and was apparently increased after administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which kills mature dopamine neurons. However, once again this result has been hard to replicate (Frielingsdorf et al 2004), and indeed other groups have only reported the in-vivo production of glia from nigral

progenitor cells, not dopaminergic neurons (Lie et al 2002).

While in-vivo studies have tended to show a restricted distribution of these cells there are many examples of in-vitro growth of neural precursor cells from a wide variety of brain regions. These studies suggest that cells in these regions have the potential to become multipotent and divide, although they tell us nothing about the true function of these cells in-vivo where they are in a completely different environment (reviewed by Anderson 2001). In non-neurogenic regions these cells may divide to create glia only, or may simply lie quiescent. If so, the question remains whether they can be stimulated to produce neurons in a similar manner to the precursor cells in other regions, and whether these neurons can provide functional benefit.

Do the new cells formed in adulthood integrate and have a functional role?

The progeny of adult rat neural stem cells have been shown to be electrically active and form functional synapses in-vitro (Song et al 2002). Several researchers have also demonstrated that the new neurons generated by adult neural precursor cells in-vivo integrate into the existing brain architecture and subsequently function (Carlen et al 2002). For example, in mice the neurons created by *hippocampal* precursor cells have been shown to integrate into existing neural circuits (van Praag et al 2002), and inhibition of neurogenesis has been seen to disrupt hippocampal-dependent learning (Shors et al 2001). It also seems that hippocampal neurogenesis is required for the behavioural response to antidepressants (Santarelli et al 2003) since x-irradiation of the mouse hippocampus prevented both the neurogenic and behavioural response. Similarly, it has been shown that inhibition of the supply of neurons destined for the *olfactory bulb* disrupts olfactory learning (Gheusi et al 2000), suggesting once again that newly formed neurons are functionally significant in adults.

Are these results applicable to man?

Eriksson and colleagues studied the brains of patients with head and neck cancer who had been given bromodeoxyuridine (BrdU, a mitotic marker) for staging of their disease (Eriksson et al 1998). They found cells in the hippocampus that double labelled for BrdU and neuronal markers (not tumour cells), suggesting ongoing neurogenesis in this region in adult life. Furthermore it has been demonstrated that multipotent stem cells can be grown from adult human brains (Roy et al 2000), even, to a limited extent, after death (Palmer et al 2001), although these in-vitro results do not tell us whether the environment prevents such behaviour in-vivo.

Despite the demonstrations of stem cell-like behaviour in the human brain we must remain cautious about the extrapolation of rodent and primate research to man. For example, it has recently been shown that the rostral migratory system is absent from human brains, and that although SVZ astrocytes can act as multipotent progenitors in-vitro there is little evidence for the production of new neurons in-vivo (Rakic 2004; Sanai et al 2004), suggesting that the environment in the adult human CNS is not permissive for this differentiation pathway. Thus it might be that spontaneous neuronal generation in man is limited to the hippocampus. However, we do not know whether stem cells found in other regions could be activated and encouraged to produce new neurons given the appropriate stimulus.

Endogenous adult neural precursor cells are responsive in-vivo

The first demonstrations that adult neural precursors could respond to *acute* brain insults were published in 1997. Kainic acid-induced seizures in the rat were shown to induce apoptotic cell death accompanied by the proliferation of cells in the hippocampus that double stained for BrdU and the neuron-specific antigen NeuN, thus suggesting the generation of new neurons (Bengzon et al 1997). Since then many other acute brain injury models have been studied, and have revealed the potential for the newly generated neurons to migrate, differentiate and provide functional benefit. For example, mice given a 6-hydroxydopamine lesion to model PD show proliferation and migration of neural precursors in their striatum (Fallon et al 2000). With intraparenchymal infusion of transforming growth factor alpha (TGFα) these precursors migrated towards the site of injury and produced a functional effect by reducing the rotational bias induced by the original lesion. In addition in a rat model of stroke the occlusion of the middle cerebral artery in adults induced cell proliferation in the SVZ, with migration of neuroblasts to the damaged striatum where they expressed markers of developing and mature striatal neurons (Arvidsson et al 2002).

Magavi and colleagues used a light-activated toxin to study the new neurons generated in response to anterior cortical apoptosis in layer VI of adult mice (Magavi et al 2000). They demonstrated that despite this relatively subtle lesion the endogenous stem cells in the SVZ lying directly beneath the cortex were stimulated to generate neurons (although some neurons may have originated from intracortical stem cells). Moreover, the neurons generated were specific for the cortical layer and region originally targeted, and many long distance cortico-thalamic projections were formed.

These results suggest that neural precursor cells can respond to acute brain lesions by migrating towards the site of damage, differentiating appropriately, forming long distance connections and possibly providing functional benefit. Furthermore, there is evidence that neural precursors can respond to a range of other factors including chronic stimuli, such as simply enriching the living environment of the animal (Kempermann et al 1997) (Table 1).

However, it should be stressed that in the above studies, the number of new neurons generated was very small. Thus the neurogenic response is inadequate to ameliorate lesions completely, and it will therefore be necessary to enhance this response if it is to be of use clinically.

Table 1 Factors known to affect in-vivo neurogenesis

↑Neurogenesis	↓Neurogenesis
Growth factors (e.g. Jin et al 2002)	Steroids (Gould & Tanapat 1999)
Antidepressants (Malberg et al 2000)	Opioids (Eisch et al 2000)
Dietary restriction (Mattson et al 2001)	Ethanol (Nixon & Crews 2002)
Physical activity (running) (van Praag et al 1999)	Antimitotics (Shors et al 2001)
Environmental enrichment (Kempermann et al 1997)	Irradiation (Monje et al 2002)
Hippocampal-dependent learning (Shors et al 2001)	Ageing (Kuhn et al 1996)
Inflammatory blockade (e.g with indometacin) (Monje et al 2003)	Dopamine depletion (Hoglinger et al 2004)
Neuropeptides (Mercer et al 2004)	
Many different experimental brain lesions (e.g. targeted apoptosis, ischaemia, seizures, trauma, MPTP, 6-OHDA (see text))	

Can we enhance the response of endogenous precursor cells to injury?

Reduce inhibition

There is recent evidence that *inflammation* may be detrimental for neurogenesis. For example cranial irradiation has been shown to reduce neural proliferation in the rat hippocampus, accompanied by changes in angiogenesis and microglial activation (Monje et al 2002). Both irradiated and non-irratiated precursors differentiated to neurons in-vitro, but neither could differentiate when transplanted into the irradiated brain, in contrast to the non-irradiated brain. This suggests that irradiation affected the cellular environment rather than the precursor cells themselves. Irradiation is known to cause inflammation, and the use of indometacin, an anti-inflammatory drug, has been shown to augment neurogenesis after irradiation (Monje et al 2003).

Furthermore the infusion of lipopolysaccharide from *Escherichia coli* has been shown to result in inflammation and microglial activation, together with a reduction in neurogenesis in the hippocampus under both basal conditions and after seizure-induced stimulation (Ekdahl et al 2003). In this experiment the administration of minocycline inhibited microglial activation and restored neurogenesis.

It is important to emphasize that the inflammatory response is complex, with temporal evolution of a range of inflammatory mediators (interleukin 6, tumour necrosis factor-α (TNF-α), nitric oxide, free radicals and so on) together with the cellular response (microglia and others). Although the above studies suggest that inhibition of some aspects of this response can promote neurogenesis it may well be that other components of the inflammatory response turn out to be essential for neural repair. For example, it is likely that localised inflammation helps generate the cytokines necessary to attract neural precursors, and may help guide their differentiation to appropriate cell types. It may be that localised cell death, not simply cell dysfunction, is necessary to provide the appropriate niche to support cell replacement.

Provide stimulation

As well as neutralising factors inhibitory to neuroregeneration, it may well be possible to enhance the response to injury by providing stimulation in the form of growth factors or neuropeptides, or by other manipulations of the host environment. In principle there are many useful ways of increasing neuronal yield, such as the promotion of stem cell proliferation, migration or survival of their progeny. Furthermore, the inhibition of stem cell differentiation towards a glial fate using noggin, a soluble bone morphogenic protein inhibitor, has proved effective at increasing neuronal yield (Lim et al 2000), as has promotion of neuronal differentiation with brain-derived neurotrophic factor (BDNF) (Benraiss et al 2001).

A wide range of growth factors have been tested with the aim of increasing the neuronal yield after injury. For example, the intraventricular administration of epidermal growth factor to mice that have suffered an experimentally-induced stroke resulted in increased neurogenesis compared with controls, with the generation of striatal interneurons (Teramoto et al 2003). Furthermore, the infusion of epidermal growth factor and fibroblast growth factor 2 to the lateral ventricles of rats following an ischaemic lesion resulted in increased generation of new hippocampal CA1 NeuN-positive neurons compared to controls (Nakatomi et al 2002). As mentioned above, TGFα may also be a promising promoter of neurogenesis (Fallon et al 2000), as might BDNF (Zigova et al 1998), or vascular endothelial growth factor (VEGF) (Sun et al 2003). In addition to growth factors there is recent evidence to suggest that neuropeptides, such as pituitary adenylate cyclase-activating polypeptide (PACAP), may be capable of stimulating adult neural stem cell proliferation (Mercer et al 2004), and the potential role of dopamine is discussed below.

As our understanding of the germinal areas of the adult brain increases so, inevitably, does the range of potential stimulants we might use to enhance neurogenesis. To this end there has been great interest in the environment of the neurogenic niche. This microenvironment contains astrocytes, which function both as stem cells and supportive cells, a basal lamina and a cocktail of molecular messengers – an area that has been the subject of recent reviews (e.g. see Alvarez-Buylla & Lim 2004). Interestingly, in the subgranular zone of the adult hippocampus the neural stem cells lie in close approximation to microcapillaries,

and there seems to be an intimate relationship between angiogenesis and neurogenesis. For example, in the adult female canary the insertion of testosterone-releasing implants results in the production of VEGF and thus endothelial cell production and angiogenesis in the higher vocal centre (HVC) of the forebrain. This angiogenic response results in increased production of BDNF from the proliferating endothelium, which in turn promotes the migration and integration of neurons from the HVC ventricular zone (Louissaint et al 2002; Palmer 2002).

So far the above models have described precursor responses to acute insults, and we do not know whether precursor cells might behave differently to *chronic* (neurodegenerative) insults, or whether the *diseased* brain is able to respond in the same way. It is essential for us to determine whether neural precursors behave differently in models of chronic neurodegeneration since these are the conditions that have so far responded best to cell replacement strategies. It might be that precursor cells themselves are adversely affected by the neurodegenerative process, or the environment of the degenerating brain might affect them.

Endogenous neural precursors and the pathogenesis of neurodegeneration

Given the distribution of neural precursors and their response to a wide range of stimuli it has been suggested that they may in fact play a role in the pathogenesis of *PD* and other neurodegenerative diseases (Armstrong & Barker 2001). The net neuronal loss seen in PD might represent a failure of repopulation resulting from deficient proliferation of the neural precursors or enhanced neural loss (beyond that which the precursors can replace). In support of this theory it has recently been reported that patients with PD have reduced numbers of proliferative cells in the subependymal zone, subgranular zone and olfactory bulb compared with controls (Hoglinger et al 2004). Any failure in the generation of neurons could itself represent altered proliferation, survival, migration or differentiation of new cells, and as mentioned could reflect the effect of the neurodegenerative process on the precursor cell itself or its environment. This would obviously have an important bearing on our ability to manipulate these cells to effect brain repair. Transgenic mice offer one way in which the progressive degeneration of PD can be modelled, and the Armstrong–Barker hypothesis tested, although typically these mice have limited cell death in the brain.

Haughey and colleagues generated transgenic mice expressing mutant amyloid precursor protein to model familial *Alzheimer's disease* (Haughey et al 2002), and demonstrated reduced proliferation and survival of neural precursors (dual labelled with BrdU and E-NCAM) coinciding with the development of amyloid plaques after 3 months of age. This seems to support the hypothesis, but researchers using APP23 transgenic mice actually showed an increase in cell proliferation in the neocortex in the transgenics, although none of the new cells were neurons (Bondolfi et al 2002), and in humans with sporadic Alzheimer's there is preliminary evidence to suggest that neural precursor turnover in the hippocampus may also be increased (Jin et al 2004).

In *Huntington's disease* (HD) the situation is also unresolved at present. For example, there is some evidence to suggest increased progenitor cell turnover and neurogenesis in the subependymal layer adjacent to the caudate nucleus in people with advancing HD (Curtis et al 2003). However, recent work from our laboratory group has shown reduced proliferation of progenitor cells in-vivo in the hippocampus of R6/1 mice (a transgenic model of HD) compared with controls (Lazic et al 2004). The jury is therefore still out, and at present the role of neural precursor cells in the pathogenesis of neurodegeneration remains to be proven.

Conclusions

Under certain circumstances the adult mammalian neural stem cell is able to up regulate cell division in order to produce offspring that can migrate towards a site of damage and differentiate to form appropriate neurons. These neurons can form axons and potentially even provide functional benefit. Despite the encouraging results discussed above this recent work must be viewed as evidence of 'proof of principle', acknowledging that there is a long way still to go (see Text box 2). In particular we must be extremely cautious in extrapolating results from one species to another since there seem to be significant differences in, for example, rodent, primate and human CNS stem cell populations.

Neurodegenerative diseases are extremely varied both in pathology and clinical presentation. Even single diseases are increasingly recognised to be heterogeneous, with diffuse pathology giving rise to a wide variety of symptoms (for PD see for example Foltynie et al 2002). As a result it is likely that patients will need to be extremely carefully selected on the basis of new clinical and pathological disease markers to benefit from a particular cell based therapy. The cell therapy must then be viewed as a treatment like many others, with benefit to some symptoms (depending on the pathology targeted) but not necessarily a 'cure'.

We are still discovering factors that stimulate and inhibit endogenous neurogenesis, and determining the extent to which the degenerating brain can repair itself. It is likely that the delivery of a cocktail of factors will be needed to optimise the production of new neurons. Furthermore, the route and method of delivery of these factors may well be critical. To this end there has been great interest in the use of viruses to transfect cells and thus deliver critical growth factors over a prolonged period of time. For example it has recently been shown that local adenovirus-induced overexpression of noggin and BDNF increased recruitment of new neurons to the adult rat neostriatum (Chmielnicki et al 2004). In this block-and-induce strategy the noggin is believed to inhibit bone morphogenic protein-induced glial cell production from the stem cell, while BDNF increases neuronal yield. In this example the virus was delivered directly to the cerebral ventricles by injection, but an appealing alternative is to transfect cultured stem

Text box 2 Hurdles to the therapeutic use of human endogenous neural stem cells

- Neural stem cells produce small numbers of new neurons in the human hippocampus, but extrapolation from animal models to human disease is not straightforward since there is little evidence for neurogenesis around the lateral ventricles in humans, and there is no obvious rostral migratory stream.
- Do 'dormant' stem cells exist throughout the human brain, and can they be stimulated to divide in-vivo?
- How many new neurons can be produced? From human embryonic allograft transplant trials it has been estimated that about 100 000 dopaminergic neurons need to survive for clinical benefit in PD.
- Can migration of new cells occur over the long distances in the human brain?
- How are cell proliferation, migration and differentiation controlled?
- How can we prevent migration and differentiation at inappropriate sites?
- Can anti-inflammatory drugs, growth factors or other manipulations improve the generation and survival of new neurons?
- Do precursor cells behave differently in the brain with a chronic neurodegenerative disease compared with normal, and can they respond to stimulation?
- Can new cells integrate to human brains to provide functional benefit?
- Can neural precursors form appropriate neurons with appropriate connections at different sites in the brain?
- What are the risks caused by stimulation of endogenous precursor cells?

cells in the laboratory. Once adequate transfection and expression of the critical genes has been verified, these cells could then be transplanted to the host where they migrate to sites of damage and integrate with existing neurons, thus potentially targeting their product to where it is most needed (for a review see Park et al 2002).

The future?

Balancing the hope from proof-of-principle studies with the reservations outlined above it is interesting to speculate what the first clinical application of endogenous stem cell repair for neurodegeneration might be.

As discussed above it seems that the dentate gyrus of the hippocampus holds the most vigorous stem cells in the human brain. Furthermore, there is evidence for an impairment of hippocampal neurogenesis in ageing, Alzheimer's disease and depression (Haughey et al 2002; Jacobs 2002; Zitnik & Martin 2002). Interestingly, there is increasing evidence that the treatment of long term stress or depression with certain antidepressants can actually reverse both the clinical mood disorder and the hippocampal atrophy (McEwen 1999; Moore et al 2000; Czeh et al 2001). As discussed above it has also been noted that anti-inflammatory drugs might enhance neurogenesis, and these drugs have been associated with a reduction in the risk of developing Alzheimer's disease (Etminan et al 2003), although this remains controversial (Breitner 2003), and no causal link to enhanced neurogenesis has been identified as yet.

In PD it has recently been reported that the reduction in dopamine in rodent models of PD decreases precursor cell proliferation in both the subependymal zone and subgranular zone (Hoglinger et al 2004) and that selective agonists of D2-like receptors restore this proliferation. These researchers also report reduced proliferation of neural precursors in postmortem brains of patients with PD. Furthermore, the subventricular infusion of a D3 receptor agonist has been reported to increase neuronal cell production in the neostriatum and subventricular zone (Van Kampen et al 2004) whereas the destruction of nigral dopaminergic neurons in a 6-hydroxydopamine mouse model of PD has been correlated with reduced proliferation of neural precursors in the subventricular zone (Baker et al 2004). It is therefore intriguing to speculate that some of the symptomatic, and possibly neuroprotective (Stocchi & Olanow 2003), effects of levodopa or dopamine agonists might result from dopaminergic stimulation of endogenous stem cells. Perhaps this goes some way to explaining why patients derive symptomatic benefit after stopping levodopa for much longer than expected from its plasma half-life (Nutt et al 2002).

Thus we may already be detecting clinical benefit from endogenous stem cell therapy, but it must be stressed that this is unproven, and even if it is the case we are a long way from the scale of repair that would be required in many more advanced cases of diffuse neurodegeneration. At present stem cell therapy is fashionable and promising. There have even been preliminary attempts at autologous neural stem cell transplantation in man (Levesque & Neuman 2002), but it is essential that we do not rush new developments to the clinic given that the basic biology is far from known, and because negative results from poorly conducted trials can have a disastrous effect on the field. The brain has evolved to have very limited plasticity; by altering this would we disrupt vital complex neural circuits, inducing dyskinesias (a problem in some patients after transplants) or disrupting memory? It is critical that if we can get the brain to fix itself this is done in a controllable and sustained fashion.

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