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ORIGINAL PAPER

Current Neurogenic and Neuroprotective Strategies to Prevent and Treat Neurodegenerative and Neuropsychiatric Disorders

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Abstract The adult central nervous system is commonly known to have a very limited regenerative capacity. The presence of functional stem cells in the brain can therefore be seen as a paradox, since in other organs these are known to counterbalance cell loss derived from pathological conditions. This fact has therefore raised the possibility to stimulate neural stem cell differentiation and proliferation or survival by either stem cell replacement therapy or direct administration of neurotrophic factors or other proneurogenic molecules, which in turn has also originated regenerative medicine for the treatment of otherwise incurable neurodegenerative and neuropsychiatric disorders that take a huge toll on society. This may be facilitated by the fact that many of these disorders converge on similar pathophysiological pathways: excitotoxicity, oxidative stress, neuroinflammation, mitochondrial failure, excessive intracellular calcium and apoptosis. This review will therefore focus on the most promising achievements in promoting neuroprotection and neuroregeneration reported to date.

Keywords Neurogenesis · Neurotrophic factors · Neural stem cells · Neurodegenerative disorders · Retinoic acid · Curcuminoids

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Introduction

Although the subject of the brain as a "renewable" organ was controversial for many years, it has been discovered that it is in fact capable of significant, yet limited, plasticity and neurogenesis. This could explain the occurrence of spontaneous rehabilitation after brain damage (Fuchs and Flügge 2014). The neurogenic potential can be defined as the ability of neural stem cells (NSCs) or neural precursor cells (NPCs), under specific conditions, to differentiate into mature central nervous system (CNS) cells such as neurons, astrocytes and oligodendrocytes (Gage 2000), and functionally integrate into the surrounding neuronal network. This allows the establishment and maintenance of polarized excitatory synaptic contacts and the restoration of the structure and function of the impaired nervous system (Fuchs and Flügge 2014; Lepski 2012; Liebau et al. 2007).

The existence of NPCs was first reported in the rodent brain (Altman and Das 1965; Altman 1962) and later isolated and successfully differentiated in vitro (Reynolds and Weiss 1992). Studies in the human brain also found the presence of these cells (Eriksson et al. 1998). While some authors defend that NPCs are present almost ubiquitously throughout the adult brain (Arsenijevic et al. 2001; Nunes et al. 2003; Richardson et al. 2006; Sanai et al. 2004), most studies report their presence in specific neurogenic sites (Kukekov et al. 1999; Leonard et al. 2009; Sanai et al. 2004), the subventricular zone (SVZ) and the subgranular zone (SGZ) in the hippocampus (Eriksson et al. 1998; Zhao et al. 2008). It is possible that, since fibroblast-like cells (FbC) are phenotipically very similar to NPCs, these (FbC) are the actual mitotic active cells found in non-neurogenic sites (Park et al. 2012). Under physiological conditions the NPCs from the SVZ and the SGZ proliferate and migrate, respectively, to the olfactory bulb and the dentate gyrus

and generate new neurons and astrocytes (Curtis et al. 2007; Doetsch and Alvarez-Buylla 1996; Lois et al. 1996). Contrary to what was initially thought, neurogenesis is a constant occurrence in these brain regions, and a large amount of experimental studies have shown that it may be altered in many neurodegenerative diseases (Lamm et al. 2014), as a possible consequence of brain aging (Bolognin et al. 2014), in stress-induced situations, or in psychiatric disorders such as depression (Conti et al. 2003; DeCarolis and Eisch 2010; Dwivedi 2009; Eisch et al. 2008; Kempermann et al. 2008; Kuhn et al. 2001; Steiner et al. 2006). While it was initially suggested that neurodegenerative diseases are confluent with a reduced precursor cell viability (Lovell et al. 2006), it was demonstrated that by using short postmortem, freshly harvested and immediately used SVZ samples, there was no significant NPC functionality reduction in elderly humans with Parkinson's disease (PD), Alzheimer's disease, progressive supranuclear palsy disease, dementia with Lewy bodies and in normal elderly control cases (Leonard et al. 2009). In fact, there are evidences that suggest that some neurodegenerative disorders such as traumatic brain injury (TBI) may even slightly stimulate neurogenesis (Curtis et al. 2003; Levin 2003; Macas et al. 2006; Richardson et al. 2007). In other words this means that even with the occurrence of such disorders, the brain still retains the capacity to generate fully functional NSCs/NPCs, which can be pharmacologically enhanced.

This knowledge has unveiled a new world of possibilities for the treatment of otherwise incurable neurodegenerative disorders. The current available therapies slow down the degenerative process but still leave the brain with irreversible damage and result in insufficient or no functional recovery. By stimulating neuron development we might be able not only to stop the progression of a disease but also to reverse its deleterious effects and therefore restore a normal cerebral function.

Neural Stem Cell Transplantation

Ever since the discovery of human embryonic stem cells (hESC) in 1998, a heavy burden of expectation has been placed upon the use of undifferentiated cells for regenerative medicine. These cells, which can be obtained from fetal precursor cells, embryonic tissues or through the reprogramming of an individual's own somatic cells, possess an unlimited self-renewal capacity which allows them to differentiate into any cell type suitable for the treatment of an unlimited variety of diseases (Ormerod et al. 2008). Cell replacement therapy by delivering specific cells to the brain can be an effective approach to treat several brain pathologies that are affected by loss of neural cells, or neural cell function as is the case of most neurodegenerative and neuropsychiatric disorders.

Fetal Neuroprecursors

Stem cell transplantation can be made primarily from fetal neuroprecursors, which have been shown to survive many years after transplantation (Mendez et al. 2005), differentiate into mature neurons (Uchida et al. 2005) and reverse some neurological deficits accompanying PD (Freed et al. 2001; Mendez et al. 2005), Huntington's disease (HD) (Capetian et al. 2009), spinal cord injury (Bohl et al. 2008), stroke (Bliss et al. 2006) and brain injury (Gaillard et al. 2007). These neuroprecursors of fetal origin can be obtained from the bone marrow, umbilical cord blood or fetal brain. However, the difficulties in obtaining these cells for scientific research, the ethical issues associated with it and most importantly the histocompatibility concerns have limited their broader use in the clinical field. As a safer alternative, the reprogramming of an individual's own somatic cells back to the pluripotent state by using oocytes has also been suggested (Tachibana et al. 2013). However, the use of oocytes still raises ethical issues and this technology is rather inefficient (Noisa and Parnpai 2011).

Embryonic Cells

Embryonic neuroprecursors have also been widely tested, and while their extremely high proliferative capacity can lead to a more efficient neurogenesis, it also hampers its use in humans due to the reported formation of malignant teratoma in 25 % of the implanted animal subjects and the inability to control their differentiation and proliferation (Boido et al. 2009; Hicks et al. 2009; Kim et al. 2002; Kim et al. 2008a, b; Maucksch et al. 2013). As an alternative, several researchers have attempted to commit the stem cells to a specific lineage prior to their transplantation, successfully converting them into specific neural cells: neural progenitor cells (Carpenter et al. 2001; Chaddah et al. 2012; Gerrard et al. 2005; Itsykson et al. 2005; Narkilahti et al. 2007; Piña-Crespo et al. 2012; Reubinoff et al. 2001; Trounson 2006; Zhang et al. 2001), neural crest cells (Lee et al. 2007a), dopaminergic neurons (Cho et al. 2008; Perrier et al. 2004), motor neurons (Erceg et al. 2010; Hester et al. 2011; Lee et al. 2007b; Zhang et al. 2011b), sensory neurons (Chen et al. 2012) and specific glial subtypes (Krencik et al. 2011). However, achieving an uniform differentiation of these cells in vitro still remains a challenge because of the many specific requirements in terms of growth factors or other small molecules for each cell subtype (Chen et al. 2012; Gerrard et al. 2005; Itsykson et al. 2005; Koch et al. 2009) and due to cluster formation

(Wichterle et al. 2002) that complicates the uniform diffusion of the substrate.

Induced Pluripotent Stem Cells

The issues that arise from the use of the previous cells can be largely resolved by using induced pluripotent stem cells (iPSC). These are obtained by transfecting mature somatic cells, from an adult source, with retroviral vectors (Takahashi et al. 2007; Wernig et al. 2008). The somatic cells are obtained from the human donor who will also later be the recipient for the differentiated cells. This method largely mitigates the occurrence of immune reactions during transplantation (Kimbrel and Lanza 2015).

Current cell-based regenerative strategies and on-going clinical trials by NSC transplantation have so far generated extremely positive results, even considering the strict regulations imposed for their manipulation. The many promising applications of the use of iPSC and hESC include ocular disorders such as macular degeneration (Schwartz et al. 2012, 2014), diabetes (D'Amour et al. 2006; Kelly et al. 2011; Pagliuca et al. 2014; Schulz et al. 2012) and heart failure (Bellamy et al. 2014; Chong et al. 2014; Menasché et al. 2015). In the neurodegeneration field, hESC have been studied for the treatment of PD and have been shown to produce fully functional and transplantable dopaminergic neurons with a long-term survival and high capacity of integrating into the surrounding neuronal network (Doi et al. 2014; Grealish et al. 2014). New studies and ongoing clinical trials are, however, focused on surpassing some challenges still encountered in the cell transplantation field. Specifically, some "rate-limiting" steps, namely long-term survival of transplanted cells, cell targeting to injured tissues and cells' successful integration in the host's organism, may delay the progress in this field. For brain delivery specifically, the successful incorporation of the transplanted stem cells in the local stem cell niche plays a decisive role in cell viability and functionality (Lepski 2012), and the interaction between the new transfected cells and the local microenvironment is still not fully comprehended. Also, like in any surgical transplantation, local inflammation and immune reaction may occur, which might compromise survival and differentiation of the engrafted stem cells (Lepski 2012). Further research in this area will not only contribute to a greater availability of therapeutic strategies in regenerative medicine but it will also be crucial to gain a better understanding of the development of the brain and the intrinsic molecular interactions that lead to the generation of specific cell types. This could enable the discovery of new compounds with neurogenic properties.

Neural Growth Factors

Given the limitations of cell replacement therapy which slow down its progress, different approaches have been explored. Several studies and human clinical trials have shown that the constituents of the microenvironments surrounding the stem cell niche and the intervening molecules in the neurogenesis process are just as fundamental as the presence of the NSCs. Probably the most important are the neurotrophic factors (NF) which are small proteins secreted by target tissues in the brain after being stimulated by the surrounding neural cells. They are capable of signaling the surrounding cells to differentiate and grow, but also of preventing them from initiating programmed cell death (Zhang et al. 2014). A large number of growth factors have been reported to possess neurotrophic properties. These include ciliary neurotrophic factor (CNTF), glial cell-line-derived neurotrophic factor (GDNF), insulin-like growth factor, fibroblast-like growth factor (FGF) and the major players in neurogenesis, the neurotrophins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) (Jagasia et al. 2009; Weissmiller and Wu 2012; Yoo et al. 2007).

The neurotrophin family of the neurotrophic factors is primarily responsible for stimulating neural cell differentiation, growth and survival, as well as controlling the brain's synaptic function and plasticity (Skaper 2012). They are produced under physiological conditions by originating neurons after receiving trophic input from their target neurotrophin-sensitive neurons with which they are connected (Thoenen 1995). Alternatively, the exposure of an autocrine or a non-target-derived paracrine neurotrophin has also been suggested. This goes for all neurotrophic factors, and while most are target- or paracrine-delivered, recent evidences have demonstrated that progranulin functions as an autocrine growth factor (Ahmed et al. 2007; Inestrosa and Arenas 2010). After release, neurotrophins are recognized by two specific receptor classes, Trks and $p75^{NTR}$, which are expressed on the surface of the neurotrophin-sensitive neurons. The neurotrophins exhibit specific interactions with the Trk receptors. TrkA binds NGF (Kaplan et al. 1991; Klein et al. 1991a), TrkB binds mBDNF and NT-4 (Klein, et al. 1991b; Squinto et al. 1991) and TrkC binds NT-3 (Lamballe et al. 1991). Under specific conditions, NT-3 can also interact with TrkA and TrkB with less affinity. All neurotrophins, however, interact with and activate the p75 receptors (Bothwell 1995; Skaper 2012), which initiate an apoptotic pathway (Chao 2003). Specifically for BDNF, its precursor (proBDNF) binds primarily to p75 receptors, therefore initiating programmed cell death. When proteolytically processed due to

neuronal activity, proBDNF is converted to mature BDNF (mBDNF) which specifically binds to the trkB receptors (Je et al. 2013) (Fig. 1). Neural survival will therefore depend on the level of neurotrophins secreted and the type of receptors expressed (Weissmiller and Wu 2012). In the CNS, due to the abundant expression of TrkB and TrkA (Weissmiller and Wu 2012) the most active neurotrophins are BDNF followed by NGF because of their high specificity for these receptors.

Given the crucial role of NFs in modulating neurogenesis in the adult brain, it is not surprising that the occurrence of most neurodegenerative or neuropsychiatric disorders is associated with an altered NF expression or their respective receptors, and several studies have successfully identified a specific NF-related cause and/or consequence for the occurrence of neurological disorders (Conti et al. 2003). GDNF and VEGF have been shown to promote the differentiation and survival of dopaminergic neurons (Eggert et al. 1999; Grandoso et al. 2007; Lindvall and Wahlberg 2008; Theofilopoulos et al. 2001; Zeng et al. 2006) and also exhibit a close correlation with motor neuron protection and reversal of degeneration (Drinkut et al. 2012; Eslamboli et al. 2005; Kells et al. 2010). In diseases associated with progressive motor impairment, like amyotrophic lateral sclerosis (ALS) and PD, these NFs are the most studied and effective in delaying the onset of neuronal and motor degeneration in rodents (Azzouz et al. 2004; Wang et al. 2002, 2007b), along with IGF (Dodge et al. 2008; Kaspar et al. 2003). NGF and BDNF have been primarily studied and mobilized toward the prevention and reversion of atrophy and loss of basal forebrain cholinergic neurons which are highly associated with brain aging dementia (Fischer et al. 1987), AD (Bruno and Cuello 2006; Connor et al. 1997; Cuello and Bruno 2007; Peng et al. 2004) and neuronal degeneration and dementia in Down's Syndrome (Castrén and Tanila 2006; Dorsey et al. 2006; Fukuda et al. 2010). Likewise, BDNF has been successful in reducing or delaying the onset of dementia in patients with Rett Syndrome (RS) (Katz 2014). Mature BDNF, as the best-characterized of all neurotrophins in terms of its role in brain plasticity, has shown to be essential for differentiation and survival of dopaminergic, cholinergic, GABAergic and serotonergic neurons (Pillai 2008) and is thus closely involved in cognition and mood-related behaviors (Cowansage et al. 2010). A decreased BDNF expression has been associated with the clinical manifestations of HD (Cattaneo et al. 2005; Zuccato and Cattaneo 2007), AD (Zhang et al. 2012) and stroke, whereas a BDNF hyperactivity has been reported in epilepsy, autism and manic-depressive disorders (Tsai 2006). Furthermore, a reduced BDNF expression occurs in stressful situations and animal models lacking BDNF expression do not respond to antidepressant treatment (Adachi et al. 2008; Monteggia et al. 2004, 2007; Saarelainen et al. 2003), which suggests a close relationship between their mechanisms of action. It has also been suggested that BDNF is involved in the respiratory control and rhythmogenesis generated and modulated in the brainstem, being therefore useful to stabilize the respiratory rhythm in respiratory disorders with a neurological cause, such as RS (Caravagna et al. 2013). FGF-2 plays a key role in angiogenesis, preventing and reducing neuronal damage

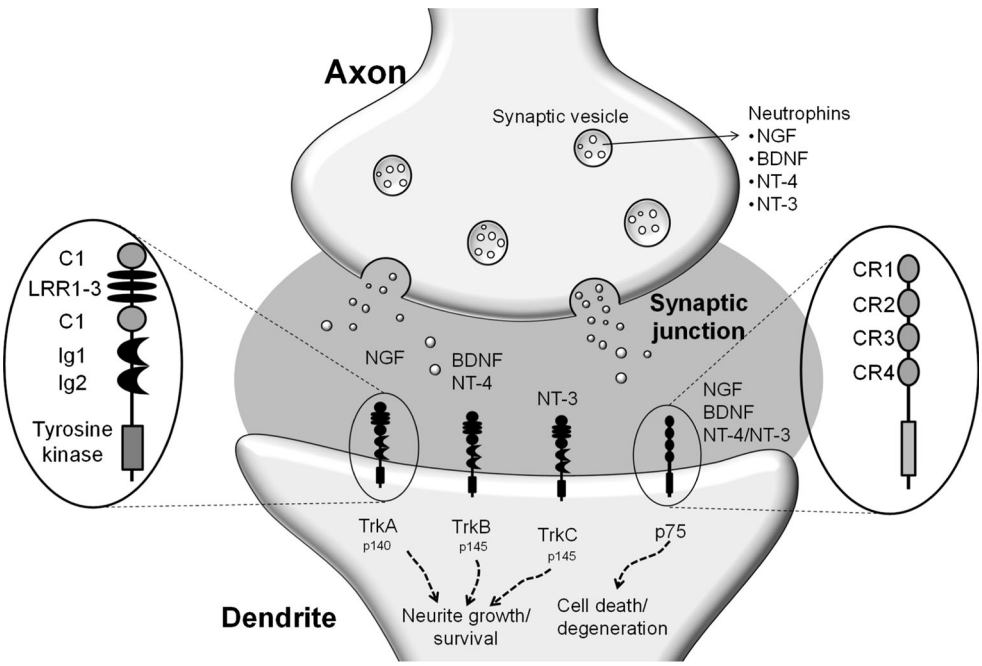

Fig. 1 Neuron growth and survival mediation through extracellular activation of Trk receptors and cell death and degeneration through extracellular activation of p75 receptors (*CR1–CR4* cysteine-rich motifs, *C1/C2* cysteine-rich clusters, *LRR1–3* leucine-rich repeats, *Ig1/Ig2* immunoglobulin-like domains, *p140* 140,000 molecular weight protein, *p145* 145,000 molecular weight protein)

after cerebral infarction (Kawamata et al. 1997), focal ischemia (Ma et al. 2008) and seizures (Liu and Holmes 1997). It stimulates a cerebral plastic response, reduces inflammation and promotes neuronal survival (Uzun et al. 2010). Another NF, P021 which is a small neutrophic compound derived from the CNTF activates endogenous neuroprotective mechanisms that could be used to treat and prevent cognitive aging (Bolognin et al. 2014).

Despite the therapeutic potential of these NF and their success in the laboratory, several drawbacks have hindered their broader use, namely their short biological half-life, rapid degradation rate and limited blood–brain barrier (BBB) permeability by oral or intravenous drug delivery (Cai et al. 2014; Herrán et al. 2014; Stankowski and Gupta 2011). All these factors result in an extremely low NF bioavailability in the brain, which is not sufficient to produce the required neutrophic effects. On the contrary, if the amount of NF administered is too high, besides the occurrence of peripheral side effects, the overstimulation of their receptors and neuronal synapses may result in epileptic seizures (Claire Géral et al. 2013), or alternatively, as several evidences suggest, it could downregulate the expression of Trk receptors therefore inhibiting their neuroprotective effect altogether (Frank et al. 1996; Knusel et al. 1997; Sommerfeld et al. 2000). The unpredictability of the amount of NF that reaches the CNS is therefore the biggest challenge to be overcome. In addition, some diseases such as stroke have a relatively short timeframe in which these NF can be effective. In order to surpass the limitations encountered in conventional drug delivery, several surgical approaches have been proposed, such as intracerebral administrations of the NFs (Kawamata et al. 1997; Kells et al. 2010; Liu and Holmes 1997; Shirakura et al. 2004; Van Kampen et al. 2014; Wu 2005; Zhu et al. 2014), the implant of programmable pumps (Grondin et al. 2002, 2003; Yanamoto et al. 2000) and the administration of gene-carrying viral vectors (Björklund et al. 2000; Choi-Lundberg et al. 1997) which, although effective, are more invasive and complex. In addition, gene therapy is irreversible. Nanoparticle-based strategies have also been explored to improve BBB permeation and promote a targeted and sustained drug release in the brain (Herrán et al. 2014; Migliore et al. 2014; Yurek et al. 2009) (Table 1). Among the many advantages offered by the use of nanoparticles, some of the most important include their ability to protect the NFs from enzymatic degradation and other stressors (Claire Géral et al. 2013), their ability to evade the host's immune system when coated with hydrophilic polymers (e.g., polyethylene glycol) (Angelov et al. 2011; Kurakhmaeva et al. 2009) with minimal loss of biological activity (Sakane and Pardridge 1997), and the possibility to target specific areas while minimizing systemic side effects (Géral et al. 2013). Furthermore, there is the possibility to anchor the surface of the nanoparticles with specific ligands toward receptor recognition in the CNS (Pang et al. 2008; Xie et al. 2005). Other more advanced strategies that have been exploited combine both of the above methods: sustained release of GDNF from encapsulated, genetically engineered fibroblasts (Sajadi et al. 2006) or genetically modified NSCs for the overexpression of NT-3 when implanted in rats (Lu et al. 2003).

While it is still difficult to deliver NFs to the brain, the wide knowledge of the molecular structure of both NFs, their receptors, and their interaction may prove useful in the design of new mimetic molecules with improved pharmacokinetic and pharmacodynamic characteristics (Webster and Pirrung 2008), as is the case of P021 which is a CNTF derivate (Bolognin et al. 2014).

Proneurogenic Molecules

Several molecules have been proposed as potential neurogenesis promoters either due to their antioxidant and anti-inflammatory properties or more specifically due to their ability to modulate neural stem cell differentiation and proliferation or apoptotic pathways. Among them, glutamate has been demonstrated to play a key role in neurogenesis in association with neurotrophic factors. It stimulates BDNF expression, which in turn modifies neuron glutamate sensitivity (Mattson 2008). However, overactivation of glutamate receptors may result in neuronal degeneration (Mattson 2008), which leads to a necessity for optimized glutamatergic signaling. Galanin, a widely expressed neuropeptide, has also been shown to exhibit an intense neuroprotective and neuroproliferative potential by modulating noradrenergic, serotonergic and cholinergic neurotransmission and by protecting neurons from excessive glutamate and amyloid β cytotoxicity (Agasse et al. 2013). However, retinoic acid, curcumin, allopregnanolone and antidepressants have received the widest attention due to their positive and very promising effects on several distinct neurogenesis pathways. A list of some of the most promising results achieved with the use of several classes of proneurogenic molecules can be seen on Table 2.

Retinoic Acid (Vitamin A)

Retinoids are a class of molecules, produced in the olfactory epithelium in the adult SVZ and hippocampus (Calza et al. 2003; Haskell and LaMantia 2005; Jacobs et al. 2006) from retinaldehyde with the enzyme retinaldehyde dehydrogenase 3 (RALDH3), which are involved in several distinct stem cell differentiation pathways (Paschaki et al. 2013) (Fig. 2). They modulate glucocorticosteroids (GCs) availability in the brain, which are released to cope with stress and are directly related to brain aging, cognitive decline, loss of brain plasticity (Cameron and Gould 1994; Suri and

Table 1 Nanosystems for neurotrophic factor delivery

Nanosystem	Disease/model	References
BDNF		
Nanoporous PGA particles	Deafness/in vitro (guinea pig)	Tan et al. (2012)
Layer-by-layer films on agarose hydrogel scaffolds	Spinal cord injury/in vitro	Mehrotra et al. (2010)
Neurotensin-polyplex nanocarrier	PD/in vitro (rat)	Martinez-Fong et al. (2012)
PEGylated cationic lipid nanoparticles	in vitro	Angelov et al. (2011)
Cubosome nanoparticles with omega-3	in vitro	Géral et al. (2012)
PLGA nanoparticles	Cauda equina syndrome/in vivo (dog)	Tan et al. (2013)
GDNF		
PLGA nanospheres	PD/in vivo (rat)	Herrán et al. (2014)
Neurotensin-polyplex nanocarrier	PD/in vitro (rat)	Martinez-Fong et al. (2012)
Trojan horse nanocarriers with brain-specific promoters	PD/in vivo (rat and rhesus monkey)	Boado and Pardridge (2011), Xia et al. (2008)
Cationic liposomes	Spinal cord injury/in vitro	Martina et al. (2008), Yang et al. (1997)
	PD/in vivo (rat)	Migliore et al. (2014)
VEGF		
PLGA nanospheres	AD/in vitro, in vivo (mice)	Herrán et al. (2013)
	PD/in vivo (rat)	Herrán et al. (2014)
Iron-oxide nanoparticles with monoclonal antibodies	Brain tumor/in vivo (rat)	Abakumov et al. (2012)
NGF		
PEGylated—PBCA nanoparticles	PD/in vivo (rat)	Kurakhmaeva et al. (2009)
Targeted liposomes	AD/in vivo	(Xie et al. 2005)
Cationic liposomes	Spinal cord injury/in vitro	Martina et al. (2008), Yang et al. (1997)
NT-3		
PBCA nanoparticles	Hypertensive intracerebral hemorrhage/ in vivo(rat)	Chung et al. (2013)
FGF-2		
Organically modified silica nanoplexes with r-FGF	Neurodegenerative disorders/in vitro	Stachowiak et al. (2009)

PGA poly-L-glutamic acid, *PBCA* poly-butyl cyanoacrylate

Vaidya 2013) and even contribute to the development of depressive symptoms (Christoph Anacker et al. 2013). In addition, it has been suggested that GCs alter BDNF expression and signaling, therefore reducing the brain's neurogenesis potential (Suri and Vaidya 2013). Thus, the modulation of GCs availability by retinoids is an important biological mechanism that can be explored in many stress-related pathologies to prevent plasticity alterations in the hippocampus (Bonhomme et al. 2014). Retinoids are also known to alleviate microglial chronic activation which occurs after brain trauma or inflammation and is associated with a progressive neurodegeneration in AD and PD and in a number of other CNS pathologies (Brossaud et al. 2013; Rangarajan et al. 2013). In addition, retinoic acid (RA) is also involved in the Wnt pathway, being therefore essential for hippocampal neurogenesis (Elizalde et al. 2011).

All-trans retinoic acid (ATRA), which is the active form of RA, has proven to be capable of inducing neuronal outgrowth and differentiation from embryonic stem cells (Lu et al. 2009; Stavridis et al. 2010; Yurek et al. 2009), NSCs (Takahashi et al. 1999; Wang et al. 2005a, b), dorsal root ganglia (Corcoran and Maden 1999) or mouse teratocarcinoma (Hádinger et al. 2009). It can be especially effective for the regeneration of neuronal cells after peripheral or CNS injury due to the increased RALDH3 expression in these situations (Santos et al. 2012).

However, ATRA is rapidly metabolized by cells, has low aqueous solubility and requires a fine-tuning of the concentration window to achieve efficacy, posing difficulties in the delivery of therapeutic doses (Santos et al. 2012). In this regard, nanoparticle formulations seem to be the most effective in promoting a prolonged ATRA release in the SVZ, and these include the use of polyelectrolyte nanoparticles (Maia et al. 2011; Santos et al. 2012), polyethyleneimine complex nanoparticles (Ku et al. 2013) and polymer-oil nanostructured carriers (Narvekar et al. 2012).

Table 2 List of some of the most relevant mechanisms of action of several proneurogenic molecules

Proneurogenic Molecule	Mechanism of action	References
All-trans retinoic acid	Reduction in oxidative stress	Nair et al. (2015)
	Promotion of NGF release	Palencia et al. (2014)
	Downregulation of NMDAR and KLF11 expression	Nair et al. (2015)
	Reduction in glucocorticosteroid expression	Christoph Anacker et al. (2013), Bonhomme et al. (2014), Suri and Vaidya (2013)
	Reduction in microglial chronic activation	(Brossaud et al. 2013; Rangarajan et al. 2013)
	Activation of the canonical Wnt/β-catenin pathway	(Elizalde et al. 2011)
Curcuminoids	Reduction in proinflammatory and oxidative responses	Mansouri et al. (2012)
	Reduction in amyloid-B aggregates	Garcia-Alloza et al. (2007), Thapa et al. (2013)
	Reduction in kainic acid-induced seizures	Sumanont et al. (2007)
	Inhibition of homocysteine production	Mansouri et al. (2012)
	inhibition of the Cu(II)-induced oxidative damage	Huang et al. (2011)
	Activation of the canonical Wnt/β-catenin pathway	Tiwari et al. (2014)
	Promotion of BDNF release in the hippocampus	Liu et al. (2014)
Neurosteroids (progesterone, alopregnanolone)	Regulation of GABAergic and glutamatergic neurons and pro-inflammatory genes	He et al. (2004), Roof et al. (1997)
	Activation of microglial cells	Pettus et al. (2005)
	Increased BDNF expression	Gonzalez et al. (2005)
	Increased activation of serotoninergic receptors	Bristot et al. (2014), Marx et al. (2003)
Antidepressants		
Fluoxetine, tranylcypromine and reboxetine	20–40 % increase in proliferative cells in the dentate gyrus and up-regulation of BDNF expression	Malberg et al. (2000)
Fluoxetine	Increased neural progenitor cells proliferation in the dentate gyrus	McAvoy et al. (2015)

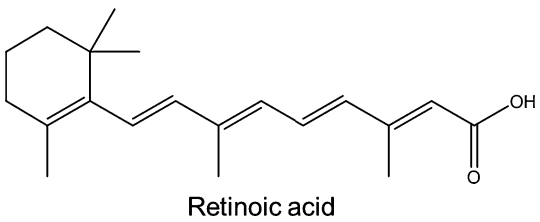

Fig. 2 Retinoic acid chemical structure

Curcumin

Curcumin is a highly pleiotropic polyphenolic molecule with anti-inflammatory, anti-amyloid, anti-apoptotic and antioxidant properties (Mansouri et al. 2012), which can be extracted from turmeric (*Curcuma longa*) (Kim et al. 2008a, b) (Fig. 3). It is involved in hippocampal neurogenesis and can enhance neural plasticity and repair (Kim et al. 2008a, b) through activation of the canonical Wnt/β-catenin pathway (Tiwari et al. 2014). In addition, due to its

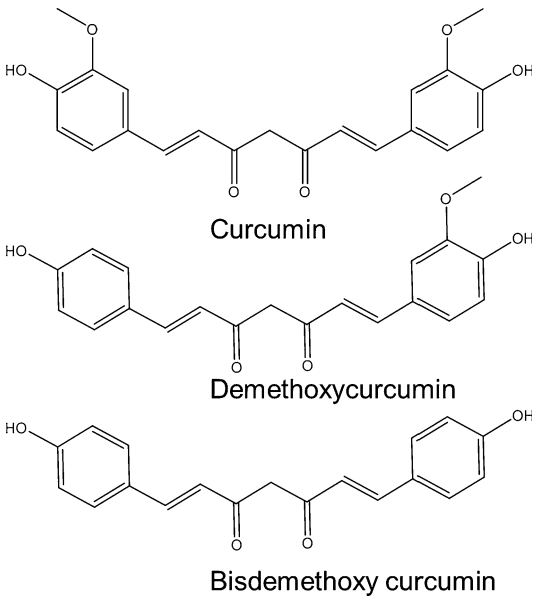

Fig. 3 Curcumin and its main analogs' chemical structure

potent anti-inflammatory potential, curcumin can also prevent neurodegeneration by inhibiting proinflammatory responses in the injured, aged or diseased brain (Wang et al. 2005a, b). It has been shown to slow the progression of AD by reducing amyloid β in the brain (Garcia-Alloza et al. 2007; Thapa et al. 2013; Yang et al. 2005). Moreover, curcumin reduces the incidence of kainic acid-induced seizures (Sumanont et al. 2007) and promotes neuroprotection in PD by reducing homocysteine production which is a risk factor for vascular disease and brain atrophy (Mansouri et al. 2012), by inhibiting the Cu(II)-induced oxidative damage (Huang et al. 2011) and by inhibiting the inflammatory glial response and reducing superoxide dismutase function in the brain (Tripanichkul and Jaroensuppaperch 2013). More recently, it has also been suggested that curcumin exhibits an antidepressant-like activity by promoting BDNF release in the hippocampus (Liu et al. 2014) and ameliorates mitochondrial dysfunctions in HD (Sandhir et al. 2014). Curcumin analogs such as demethoxycurcumin and bisdemethoxycurcumin, which can often be found in curcuminoid commercial powders, have also been reported to possess considerable antioxidant, anti-inflammatory and anti-proliferative activities (Kim et al. 2001; Sandur et al. 2007; Simon et al. 1998) (Fig. 4).

The neuroprotective efficacy of curcumin is, however, limited by its low brain bioavailability due to poor absorption, rapid metabolism and systemic elimination, and limited blood brain barrier (BBB) permeability (Yang et al. 2007). Therefore, the production of curcumin-loaded nanoparticles for brain delivery has been increasingly reported, namely the use of liposomes and phospholipid complexes (Tsai et al. 2011), biodegradable poly(lactic-co-glycolic acid) (PLGA) nanoparticles (Tiwari et al. 2014; Tsai et al. 2011) and liposomes (Chiu et al. 2013), which allow for a superior bioavailability and BBB permeability, reduced elimination and a slow and sustained curcumin release in the SVZ.

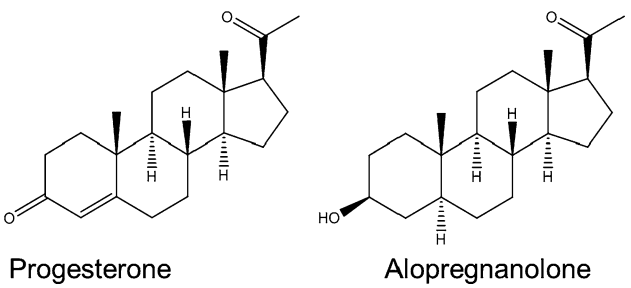

Fig. 4 Progesterone and pregnanolone's chemical structure

Neurosteroids

Neurosteroids, which are steroids produced in the brain, regulate physiological functions in the CNS. Among them, pregnane neurosteroids, such as progesterone (PROG) and its metabolite allopregnanolone, (AP) have been receiving increasing attention due to their neuroprotective effects in several neurodegenerative and neuropsychiatric disorders (Fig. 4). PROG and AP regulate both GABAergic and glutamatergic receptors and are also known to prevent lipid peroxidation, the generation of isoprostanes (Roof et al. 1997), the expression of pro-inflammatory genes (He et al. 2004), the activation of microglial cells (Pettus et al. 2005), and of regulating BDNF expression (Gonzalez et al. 2005). PROG has also been reported to regulate the expression of anti-apoptotic proteins, such as Bcl-2 (Bristot et al. 2014). Several in vitro and in vivo preclinical studies have demonstrated AP's high potency and efficacy in promoting neurogenesis in aged brain and in the neuronal restoration after TBI (He et al. 2004), AD (Brinton and Wang 2006a, b) and posttraumatic stress disorder (Pibiri et al. 2008). Studies in humans have primarily shown a correlation between the downregulation of AP biosynthesis and the occurrence of psychiatric symptoms ranging from anxiety and depression (Uzunova et al. 1998), aggressiveness (Bristot et al. 2014), schizophrenia (Marx et al. 2003) and bipolarity (Johansson et al. 2011) due to their effect on serotoninergic receptors. Additionally, even though AP has the advantage of being a small hydrophobic BBB penetrating molecule (Brinton and Wang 2006a), it is quickly inactivated by glucuronidation, sulfate conjugation and oxidation (Bristot et al. 2014).

Antidepressants

The potential influence of psychoactive drugs in brain neurogenesis is a very widely studied area, and while it has been demonstrated that opioids and alcohol negatively influence neurogenesis (Canales 2007; Crews and Nixon 2003; Eisch et al. 2000), antidepressants (ADPs), atypical antipsychotics and mood modulators have been shown to positively impact neurogenesis (Duman et al. 2001a; b; Harwood 2003; Malberg 2004; Wakade et al. 2002). There is evidence which suggests that stress-induced neurobiological disorders are highly associated with a decreased production of NFs or abnormalities in their receptors (Dwivedi 2009), hippocampal morphological alterations including atrophy and loss of CA3 pyramidal neurons (McEwen 1999). While these are not the sole cause for the occurrence of these disorders, they are likely major contributors. Therefore, it has been demonstrated that ADPs possess neuroprotective and neuroregenerative effects by mediating the expression of neurotrophic and protective factors such as bcl-2, BDNF and NGF (Croce et al. 2014), and by regulating the glucocorticoid receptor

function (Anacker et al. 2011). Some ADPs also increase AP expression in rodents and the levels of neurosteroids in depression and panic disorders (Bristot et al. 2014). Some authors report, however, that ADPs such as the widely studied fluoxetine (serotonin-reuptake inhibitor) have a small influence on hippocampal neurogenesis when compared to increased exercise in mice, and in some cases, such as for duloxetine (dual serotonergic-noradrenergic reuptake inhibitor) show no increased neuron regeneration or survival (Hanson et al. 2011; Marlatt et al. 2010). Although the exact mechanism of action of ADPs in neuroprotective and neuroregenerative processes is still not fully comprehended, therefore eliciting conflicting opinions on the subject, it is common knowledge that due to their ability to revert neural impairment either by reducing stress or by actively promoting neuron generation and proliferation, these molecules are very promising in the regenerative medicine field.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) refers to the use of oxygen as a therapeutically active substance, at a superior level than the atmospheric pressure (Mu et al. 2011). The temporary elevated partial oxygen pressure in the body leads to a superior erythrocyte transporting capacity and tissue regenerating processes. Therefore, it was initially used for the treatment of diabetic foot, crush injuries, skin grafts, thermal burns and several neurological diseases (Mychaskiw 2010). However, since neurons are highly energy-demanding and require a constant oxygen supply (Mu et al. 2011), several studies have supported HBOT's further applicability for the treatment and prevention of neurodegenerative disorders (Godman et al. 2010; Günther et al. 2005; Wang et al. 2009; Zhang et al. 2010, 2011a). Although there is yet a lot to be learned about its underlying mechanisms of action, HBOT's neuroprotection and neurogenic potential have been correlated with the activation of several signaling pathways and transcription factors, such as the Wnt, hypoxia-inducible factors (HIF) and cAMP response element-binding (CREB). HBOT's neuroprotective potential by the Wnt pathway is thought to be regulated by decreasing the negative influence of β-catenin in cell proliferation (Wang et al. 2007a; Zhang et al. 2011a). Similarly, inhibition of HIF through HBOT also triggers β-catenin's reduced expression (Mazumdar et al. 2010; Milosevic et al. 2009). It has also been suggested that HBOT blocks CREB's degradation (Mu et al. 2011), which is involved in the up-regulation of BDNF, VEGF and Bcl-2 genes (Zhu et al. 2004). Therefore, HBOT, in addition to increasing oxygen supply to the brain, also promotes NSC proliferation and differentiation into neurons and oligodendrocytes, which makes it useful for the treatment of neurodegenerative conditions such as stroke (Lee et al. 2013; Shin et al. 2008; Yin and Zhang 2005; Yin et al. 2003) and TBI (Kernie and Parent 2010; Rockswold et al. 2007). Certain physiological abnormalities including cerebral hypoperfusion, inflammation, mitochondrial dysfunction and oxidative stress that occur in autistic individuals and lead to neurodegeneration may also be ameliorated by HBOT therapy (Jepson et al. 2011; Rossignol et al. 2009; Sampanthavivat et al. 2012). HBOT's role in other conditions has also been studied, namely in AD by reducing cell toxicity and oxidative stress (Tian et al. 2012) and cerebral palsy by improving brain oxygenation and ameliorating the motor function (Mukherjee et al. 2014).

Conclusion

Current advances in the field of neurobiology are allowing a better understanding of the role of NPCs in brain renewal after traumatic or ischemic brain injury and in several neurodegenerative and neuropsychiatric disorders, such as Alzheimer's disease, PD, Huntington's disease, autism, bipolar disease, among many others. The most promising approaches for stimulating neurogenesis include the transplantation of NSCs programmed toward a specific cellular line, the administration of neural growth factors, namely neurotrophic factors, the administration of proneurogenic molecules and the use of hyperbaric oxygen therapy. Although stem cell therapy has been on the verge of incredible breakthrough, therapy with proneurogenic molecules due to fewer limitations for its use will most likely evolve more rapidly. It is also possible to ally this strategy with hyperbaric oxygen therapy which would potentiate the results. There are still several significant setbacks to be overcome in order for a successful treatment of these debilitating disorders to be achieved, which means that a lot remains undiscovered. However, considerable progress has been made, and these advances will lead to new technologies and innovative therapies which will undoubtedly make a huge change in society.

Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest and have no proprietary or commercial interests in any concept or product discussed in this paper.

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