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From Neurotransmitters to Neurotrophic Factors to Neurogenesis

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Abstract

New neurons continue to be produced in adult mammals, including humans, predominantly in the anterior subventricular zone of the lateral ventricle and the subgranular zone of the dentate gyrus. This update focuses on the emerging concept that adult CNS neurogenesis can be regulated by targeting neurotransmitter receptors, which in turn drive expression of crucial neurotrophic and growth factors. Such an approach might enable the development of pharmacological treatments which harness the endogenous potential of the CNS to replace lost cells in neurological disorders such as stroke and Alzheimer's and Huntington's diseases. This review samples *in vivo* studies in adult mammals from 2006 to mid-2008. It also provides some considerations for navigating towards translation to human disorders. Among them are the formidable problems of scaling up production of new neurons within the two “niches” of the brain and delivering sufficient numbers to distant degenerating regions for cell replacement. However, an expedition can only succeed if started.

The excitement about adult neurogenesis continues to gain momentum as is evident from the exponential growth in publications to over 400 in 2007 (Fig. 1). Besides its intriguing cell biology and persistence of plasticity, adult neurogenesis generates the hope that people with neurological disorders might some day benefit from its study and utilization (Ormerod and others 2008; Ohab and Carmichael 2008). This update includes *in vivo* studies in mammals from 2006 to mid-2008 and covers the emerging concept of regulating endogenous adult CNS neurogenesis by pharmacologically targeting endogenous mechanisms. Other reviews provide more extensive coverage about the regulation and function of adult neurogenesis (Hagg 2007; Gage and others 2007; Lledo and others 2008; Zhao and others 2008) and the promise of new oligodendrocytes for demyelinating disorders (Miller and Mi 2007).

Neurogenic niches in adult CNS

In mammals, adult neurogenesis in the CNS occurs in the subventricular zone (SVZ) of the anterior regions of the lateral ventricle and in the subgranular zone (SGZ) of the dentate gyrus on each side of the brain (Fig. 2,3). The dentate gyrus and hippocampus together form the hippocampal formation, thus the term “hippocampal” neurogenesis. Neurogenesis can be increased with therapeutic agents such as neurotrophic factors and neurotransmitter drugs (Fig. 4; and see below). In rodents, new immature neurons, called neuroblasts, from the SVZ migrate through a distinct rostral migratory stream to the olfactory bulb. There, some of the neuroblasts mature and integrate with the neuronal circuitry whereas others die. In the SGZ, the new neurons migrate over a very short distance into the neighboring granule cell layer where some become functioning neurons. The functional significance of the new neurons is becoming more clear and seems to include olfactory function and certain forms of memory (Zhao and others 2008; Lledo and others 2008). The link between reduced hippocampal neurogenesis and

depression, which has received much attention lately, remains to be resolved (Kempermann and others 2008; Thomas and Peterson 2008).

Neurogenesis also occurs in adult humans but it is still debated whether rostral migration of neuroblasts exists (Curtis and others 2007). The exact location of the neural stem cells in humans has not been determined, although neuroblasts seem to be present only in the wall of the anterior horn and body of the lateral ventricles (Quinones-Hinojosa and others 2006). One obvious difference between humans and rodents is the size (Fig. 2), which may or may not prove to be a barrier to utilizing adult neurogenesis for human disorders involving more distant regions of the brain. Another difference is the apparent low proliferation rate in humans (Quinones-Hinojosa and others 2006).

Neurotrophic factors, growth factors, neural cytokines and neurogenesis

Historically, proteins that bind to transmembrane receptors have been divided into categories such as neurotrophic factors, cytokines, growth factors etc. Depending on the cell type or context, many of these proteins can exert a variety of effects on cells, ranging from proliferation to maturation and trophic support. In this review, the term neurotrophic factor includes all of these factors.

Among the neurotrophins, brain-derived neurotrophic factor (BDNF) is known for its survival-promoting effects on new neuroblasts through the TrkB receptor (Bath and others 2008). Interestingly, knock-in of a human BDNF single-nucleotide polymorphism (V66M) in mice reduces activity-dependent release of BDNF and neurogenesis in the SVZ resulting in reduced olfactory function. Whether this BDNF variant affects human neurogenesis remains to be determined. BDNF and nerve growth factor (NGF) can also act through the common p75 receptor found on a sub-population of highly proliferative precursor cells in the SVZ (Young and others 2007). This raises the possibility of utilizing small molecule p75 mimetics to promote neurogenesis. NGF also enhances survival of new hippocampal neurons, most likely by increasing cholinergic tone (Frieglingsdorf and others 2007). The effects of the two other mammalian neurotrophins had not been investigated in vivo until recently. NT-4, which also signals through TrkB, appears to be redundant as its knock-out in mice does not affect baseline or ischemia-increased neurogenesis (Rossi and others 2006). On the other hand, this does not mean that endogenous NT-4 could not be utilized to regulate neurogenesis. Data from conditional knock-out mice suggests that neurotrophin-3 (NT-3) promotes hippocampal neurogenesis and the related long-term potentiation (LTP) and spatial memory (Shimazu and others 2006).

Basic fibroblast growth factor or FGF-2 is well-known for its mitotic effects in neurogenesis. Data from conditional FGF receptor 1 knock-out mice suggest its role in hippocampal neurogenesis, LTP and memory consolidation, but not spatial memory (Zhao and others 2007). New dentate gyrus cells have different and sometimes opposing roles in different types of memory as shown after ablation of neurogenesis (Saxe and others 2007a). These studies re-emphasize the complexity of the contribution of neurogenesis to cognitive function and serves as a reminder of the potential pit-falls of translation to humans.

The transforming growth factor (TGF) family plays an important role in neurogenesis. TGF α is the endogenous epidermal growth factor (EGF) receptor ligand. Infusion of TGF α plus Noggin, a suppressor of gliogenesis, into the dopamine-depleted striatum of adult rats generates a large number of multipotent neural progenitors that migrate into the striatum (de Chevigny and others 2008). However, no new neurons were produced, pointing to the need to combine such treatments with maturation-inducing agents. Little knowledge exists about the latter and may prove to be a difficult task when considering the need to induce specific neuronal phenotypes as well as appropriate integration into existing or surviving neural networks.

Transgenic overexpression of TGF β 1 from astrocytes in mice reduces hippocampal neurogenesis (Buckwalter and others 2006). This suggests that TGF β 1-inhibiting agents might promote neurogenesis. Adding to the list of factors, infusion of glial cell-line derived neurotrophic factor (GDNF) into the post-ischemic striatum promotes SVZ proliferation, recruitment of neuroblasts into the striatum and survival of new neurons (Kobayashi and others 2006).

The vasculature may prove to be a useful target or entry point for therapeutics that induce adult neurogenesis. The angiogenic response to injury is associated with increased levels of various vascular growth factors including vascular endothelial growth factors (VEGFs) and angiopoietin-1 (Ang-1). These proteins directly or indirectly promote survival of newly arrived neuroblasts, attracted by the vascular released stromal-derived factor-1 (SDF-1; Ohab and Carmichael 2008). The finding that many neuroblasts migrate along blood vessels (Bovetti and others 2007) suggests that the vascular mechanisms could be manipulated to guide neuroblasts to ectopic regions. Erythropoietin (EPO) and its receptor play important roles in SVZ neurogenesis and its response to stroke, as shown in conditional knock-out mice (Tsai and others 2006). It will be important to determine how these responses can be enhanced or regulated for maximal benefit. The advantage of harnessing the injury-induced vascular responses would be their presence mainly in damaged regions where cell replacement is needed most. Neurogenesis occurs in humans following forebrain ischemia (Macas and others 2006). It will also be important to determine whether the vascular responses occur in other models and other disorders. The advantage of targeting the vasculature is the relative ease of administering therapeutic agents (e.g., i.v.) and the accessibility of drugs, particularly proteins, that have a poor penetration into the CNS tissue.

Neural cytokines constitute a family of neurotrophic factors, including ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF; Bauer and others 2007). CNTF plays an important role in adult CNS neurogenesis as evidenced by reduced neurogenesis in CNTF knock-out mice and in mice infused with neutralizing antibodies (Yang and others 2008). Increased neurogenesis after perinatal hypoxia/ischemia seems to be related to increased LIF, but not CNTF, in the SVZ (Covey and Levison 2007), possibly because CNTF expression develops during the second postnatal week. CNTF levels increase in most acute adult models of disease, but it remains to be determined whether this plays a role in increased neurogenesis in stroke and other models. Interestingly, diabetic db/db mice have an attenuated CNTF response to ischemia (Kumari and others 2007), perhaps explaining the diabetic risk factor for stroke outcomes.

Several other proteins such as sonic hedgehog, notch and ephrins are also known to regulate adult CNS neurogenesis. Of particular interest is the finding in knock-out mice that astrocyte-derived ephrin-A2 and A3 outside the SVZ and SGZ are negative regulators of neurogenesis in the CNS (Jiao and others 2008). This suggests that inhibition of these ephrins selectively in regions where cells need to be replaced could lead to beneficial ectopic neurogenesis.

Neurotransmitter regulation of neurogenesis

Several neurotransmitter systems regulate adult CNS neurogenesis. Serotonin (5-HT) plays a clear role and neurogenesis can be increased with serotonin re-uptake inhibitors such as the anti-depressant fluoxetine (Prozac), which targets early progenitor cells but not the neural stem cells (Encinas and others 2006). Whether targeting one cell population over another ultimately has an advantage remains to be determined. Dopamine is also known for its effects on neurogenesis. For example, D2 dopamine agonists can increase neurogenesis in mice and in mouse parkinson models (Borta and Hoglinger 2007; Yang and others 2008). Another monoamine, noradrenaline, probably only plays a role in adult hippocampal neurogenesis

because of the sparse noradrenergic innervation of the SVZ. An $\alpha 2$ -adrenergic agonist increases hippocampal neurogenesis by increasing survival and differentiation of new neuroblasts possibly by increasing BDNF in local noradrenergic afferents (Rizk and others 2006). This effect involves increased noradrenaline release by blocking pre-synaptic receptors, perhaps limiting the utility of this approach in disorders such as Alzheimer's disease in which these fibers degenerate. With many receptor sub-types and prominent side-effects in humans it will be important to determine which monoaminergic agonists or antagonists would be most beneficial in particular diseases.

Glutamate also plays a role in neurogenesis. For example, kainic acid excitotoxicity increases hippocampal neurogenesis in a cannabinoid CB1-dependent manner (Aguado and others 2007). Different sub-classes of SVZ neuroblasts are affected through kainate and metabotropic receptors, both by increasing calcium levels (Platel and others 2008). This adds to the evolving understanding that there are different populations of neural stem cells and neuroblasts in the CNS (Merkle and others 2008). This may seem like a challenge, but it might open the way to selectively produce sub-populations of neurons. The inhibitory transmitter, GABA, is also well-known for regulating neurogenesis. Interestingly, GABA is essential for activity-dependent neurogenesis and synaptic integration (Ge and others 2007). GABAergic transmission and neurogenesis in the SGZ may be facilitated by co-release of SDF-1 (Bhattacharyya and others 2008). The convergent cooperation between glutamate and GABA in adult CNS neurogenesis is becoming clear (Platel and others 2008). However, given the general and important role of these transmitters to CNS function, the use of selective agonists to different receptor types will be required. Targeting specific receptor combinations most likely will provide a refined method of directing genesis of appropriate types of neurons and their functional integration.

Neurotransmitter regulation of neurotrophic factors

One approach to developing pharmacological treatments is to determine how endogenous proteins can be regulated by neurotransmitter agonists and antagonists. One advantage is that neurotransmitter-based drugs are already widely used in clinical practice for a large number of diseases and their dosing and safety has been established. The ability of serotonin to stimulate BDNF expression is well-known. A serotonin re-uptake inhibitor can increase BDNF and neurogenesis, and neurogenesis-mediated improvement in motor function in a mouse model of Huntington's disease (Duan and others 2008). This suggests that at least in that model, and perhaps in the human disease, stimulation of BDNF remains possible. The tri-neuropeptide VGF is among the genes that are regulated by both 5-HT and BDNF and has both neurogenic and anti-depressant effects in mice, suggesting that it is downstream of BDNF (Thakker-Varia and others 2007). VGF is among a growing list of neuropeptides that affect neurogenesis, providing additional opportunities for developing treatments selective for sub-populations of precursor cells. Other neurotransmitters also increase BDNF expression and neurogenesis at the same time, as shown by an $\alpha 2$ -adrenergic agonist (Rizk and others 2006), and kainic acid (Aguado and others 2007). Of interest is the finding that the increased expression of BDNF after treatment with the nitric oxide inhibitor, L-NAME, is dependent on rhythmic diurnal corticosterone levels (Pinnock and Herbert 2008). This might mean that treatments targeting certain mechanisms require intermittent dosing. This may also be relevant to multiple sclerosis where patients are treated continuously with high levels of corticosteroids over a period of time. The idea of intermittent treatment is also suggested by the apparent discrepancies between D2 dopamine or $\alpha 2$ -adrenergic agonists and antagonist on adult neurogenesis, which may depend on acute vs. chronic administration (e.g., Yang and others 2008 vs. Kippin and others 2005 and Lonngren and others 2006 vs. Rizk and others 2006).

Neurotransmitters can also regulate expression of other factors in concert with neurogenesis. Intermittent treatment with nicotine stimulates nicotinic cholinergic receptors and promotes SVZ neurogenesis by increasing FGF-2 and via the FGF receptor 1 (Mudo and others 2007). This treatment does not increase hippocampal neurogenesis, one of several examples of different mechanisms in the two regions. This should help to develop treatments that can target neurogenesis in either region. Kainic acid also seems to regulate neurogenesis via FGF2, in a cannabinoid receptor-1 dependent manner (Aguado and others 2007). Status epilepticus, which has a large glutamatergic component, increases hippocampal neurogenesis in an IGF-1-dependent manner (Choi and others 2008). Interestingly, IGF-1 was present in neighboring activated microglia, adding to the growing evidence for an important role of these cells in neurogenesis (Walton and others 2006).

CNTF is expressed almost exclusively in the nervous system and has potent neurotrophic and other biological effects. This provides a unique opportunity because oral drugs that cross the blood-brain-barrier and stimulate CNTF levels would circumvent the low CNS penetration and serious side effects of systemic CNTF injections seen in clinical trials for ALS. We have shown that the dopaminergic pathway to the striatum regulates CNTF and regulates neurogenesis only through CNTF (Yang and others 2008). Moreover, a D2 agonist increases neurogenesis by stimulating CNTF expression. Other drugs most likely also can have such effects, as treatment with an α 2-adrenergic agonist further induces CNTF in Muller cells after retinal ischemia (Lonngrén and others 2006). CNTF is not regulated uniformly throughout the CNS, as a D2 dopamine agonist increases CNTF in the brain but not the spinal cord (Yang and others 2008). It will be important to understand which types of neurotransmitter drug treatments would lead to the greatest CNTF-mediated increases in neurogenesis after different types of injuries in different CNS regions.

One of the problems with utilizing neurotransmitter systems is their degeneration in many disorders. One solution seems to be to target astrocyte-mediated mechanisms that do not depend on the more vulnerable neurons in and around the neurogenic regions or on afferents and their synapses. Astrocytes have a number of neurotransmitter receptors (Cahoy and others 2008). However, a great deal more information about the role of different glial neurotransmitter receptors in neurotrophic factor production and their responses to different treatment regimens is needed. Astrocytes produce VEGFs, FGFs, TGFs, IGF1, CNTF, neurotrophins, GDNF and several other factors (Cahoy and others 2008). However, it is unclear which one of the astroglial factors would be most beneficial under which pathological conditions. Some of these factors, including the VEGFs, TGF α , TGF β 2, and TGF β 3 are enriched in astrocytes vs. neurons and oligodendrocytes (Cahoy and others 2008). This suggests the existence of molecular regulators that selectively increase the expression of these factors in astrocytes and which might therefore be selective drug targets. CNTF may have the advantage of being expressed almost exclusively in the nervous system. However, it is expressed widely throughout the CNS and is abundant in the Schwann cells of the PNS. As proposed before (Hagg 2005), targeting overlapping receptor systems might reduce the potential side-effects that could be associated with increased CNTF levels in particular regions of the nervous system. Maximal levels of neurogenesis might be obtained by stimulating expression of multiple protein factors and/or targeting mechanisms in different cell types (Fig. 5). It will be important to determine which receptors regulate expression of which neurotrophic factors in which cells.

Considerations for navigating towards clinical translation

The idea that adult CNS neurogenesis might be harnessed through pharmacological means as treatments for human disorders is at this moment simply that, an idea. How will it be possible to produce sufficient numbers of new neurons and do this over an extended time period while the original “old” neurons continue to die? How would one know when sufficient numbers of

new neurons have been produced to provide lasting benefit? Will new neurons be affected by the disease process? Will the new neurons become integrated and functioning or will they simply provide trophic support for the old ones? These are but a few of the many unanswered questions. One could argue that transplantation of neural stem cells would solve some of these problems. However, transplantation has numerous drawbacks too, some of them similar, some of them different from the “endogenous” approach. At this time it would be premature to choose one therapeutic approach over another. In fact, studying both allows for exchange of knowledge and faster progress towards cell replacement therapies for human disorders.

Is there a disease that represents a “low-hanging fruit” in terms of endogenous cell-based therapies? Huntington's disease is characterized by degeneration of GABAergic neurons in the neostriatum. New neuroblasts in the neighboring SVZ already have GABAergic properties and the migration distance for new neurons into the caudate nucleus would be relatively short. Animal studies seem to indicate a robust response to infusion of neurotrophic factors, but few mature neurons are actually formed, with even fewer making appropriate new axonal connections with distant targets. Alzheimer's disease affects the hippocampal formation, among many other regions. Certain forms of memory seem to be affected by the new neurons in the dentate gyrus. However, cognitive decline in Alzheimer's disease is most likely a result of degenerating synapses in a large number of brain regions, involving multiple neurotransmitter systems. It is at this point premature to conclude that new neurons in the dentate gyrus would be beneficial or not in Alzheimer's disease. The potential to utilize endogenous neurogenesis as a treatment for stroke is being investigated in a number of laboratories. The daunting task facing us is reflected by the vast numbers of new neurons needed to reconstitute the lost neurons in most strokes that cause neurological deficits in humans. The other is the vast distance between the SVZ or SGZ and many of the common areas affected by stroke. The recent finding that ephrins may repress neurogenesis in the rest of the brain (Jiao and others 2008) may provide an inroad into solving this problem, e.g., by administering ephrin inhibitors into affected regions.

Among the cellular mechanisms that can be targeted are proliferation of stem cells/progenitors and survival of new neuroblasts and neurons. Some proteins affect one and not the other. Targeting only survival would have the disadvantage of being limited to the endogenous rate of proliferation, which in humans seems to be low (Quinones-Hinojosa and others 2006). When promoting proliferation, the concern of tumors arises.

Neurotransmitter drugs have drawbacks, including side-effects, particularly in disorders characterized by degeneration of neurotransmitter pathways. One potential solution might be to use low doses of multiple drugs that target receptors which overlap predominantly in the region of interest. Another problem is that many neurogenic drugs are agonists. When agonists are given chronically many receptors change their sensitivity, including becoming desensitized. Intermittent dosing protocols might address this problem. Alternatively, antagonists are less known for de-sensitization, but much more knowledge about their effects on neurotrophic factor expression is needed. It will also be important to identify combinations of drugs whose neurogenic capacity involves modulation of neurotrophic factors with ones that do not (Fig. 5). By targeting two different mechanisms, such an approach is expected to provide an additive effect on stimulating neurogenesis. Finally, there is a need for drug screening to identify more effective and neurogenesis-selective compounds (Longo and others 2006; Saxe and others 2007b). Those should include FDA-approved drugs, as their clinical testing would be relatively easy.

There is a growing interest in the role of exercise, caloric restriction, intermittent fasting and environmental enrichment, in adult CNS neurogenesis. They appear to regulate some of the same molecular mechanisms discussed above. These and other non-pharmacological methods

could very well play a role in therapies for humans, either alone or adjuvant to drug treatments or cell transplantation.

So, are we there yet? To take Columbus' expedition as an example, land is not in sight yet. Perhaps we have not even left the harbor. However, we are sailing and are excited about discovering this potential new territory in human medicine. Importantly, the knowledge gained while traveling will be of great value to other ventures.

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Figure 1. Adult neurogenesis publications skyrocket

The number of publications (as a percentage of 2007) retrieved in a PubMed search using the keywords “adult” plus “neurogenesis” or “neurotransmitter” plus “neurogenesis” shows an exponential growth in the field. Neural stem cells of the adult mammalian CNS were identified in 1992.

Figure 2. Adult CNS neurogenesis occurs in two hot-spots

Substantial levels of proliferation and neuroblast formation (yellow dots) are present almost exclusively in the SVZ of the front of the lateral ventricles (blue) and in the SGZ of the dentate gyrus in the hippocampal formation (red). SVZ neuroblasts migrate to the olfactory bulb through the rostral migratory stream (purple), most evident in rodents. The difference in size between the human brain and those of mice and rats (top right corner) illustrates one of the potential difficulties of targeting endogenous adult neurogenesis for cell replacement therapies.

Figure 3. Astrocytes are essential for adult SVZ and SGZ neurogenesis

Schematic inset in A) shows coronal sections through a rodent brain to illustrate the location of the neurogenic regions. Blue indicates the ventricles. **A)** In the dentate gyrus, where new neuroblasts are born in a thin ribbon just inside the granule cell layer (GCL), proliferation is evident by incorporation of systemically injected BrdU into the replicating DNA. The new neuroblasts migrate into the GCL and some integrate among the mature neurons (nuclear neuronal marker NeuN). **B)** Astrocytes (GFAP marker) are closely interspersed with the proliferating cells and neuroblasts and play an important role in neurogenesis. A small sub-set of astrocytes are thought to be the neural stem cells. **C)** The SVZ is located on the lateral side of the lateral ventricle (LV) neighboring the neostriatum (NS; caudate-putamen). In humans,

the SVZ neighbors the head of the caudate nucleus. CC = corpus callosum. **D)** Precursor cells with BrdU-labeling are intimately associated with astrocytes. **E)** The astrocytic processes form a dense scaffold or meshwork that is limited to the SVZ and forms a tube-like structure in the rostral migratory stream (RMS). This enables close regulation of neurogenesis and neuroblast migration. **F)** New neuroblasts migrate through the RMS as shown here by Dil tracer that they took up in the SVZ after injection into the lateral ventricle. **G)** GFAP-positive astrocytes produce CNTF, as shown by the almost exclusive overlap in immunofluorescent staining, resulting in a yellow color (as in Yang et al., 2008). CNTF is one of the endogenous stimulators of neurogenesis.

Figure 4. Neurogenesis can be increased with neurotrophic factors and neurotransmitter drugs
The left panels show that CNTF injection into the adult mouse brain increases the number of proliferating cells in the dentate gyrus as seen by incorporated BrdU. PBS = phosphate buffered saline control. GCL = granule cell layer. The right dark-field panels illustrate the neurogenic effects of a treatment with a D2/3 dopamine receptor agonist in the adult rat SVZ. LV = lateral ventricle.

Figure 5. Multiple drug targets can regulate neurogenesis

Our recent work shows that the dopaminergic projections from the midbrain regulate neurogenesis by stimulating D2 receptors and by inducing CNTF expression in astrocytes. Systemic treatment with D2 agonists induces neurogenesis by inducing CNTF. Other neurotransmitter systems most likely also regulate neurotrophic factor production by astrocytes, thereby regulating neurogenesis. Astrocytes are more resistant to injury in most neurological disorders, making them good drug targets for enhancing neurogenesis. Neurotransmitter receptors are also present on the precursor cells and other cell types in the neurogenic niches and also contribute to the overall regulation of this complex biological process. Therefore, by combining different drug types, greater numbers of new neurons might be produced and a more refined level of control over the neuronal phenotype fate might be exerted. Such pharmacological drugs would ideally be given oral, given over extended periods and have acceptable side-effects.