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Chapter I

Seizure-Induced Neurogenesis in the Dentate Gyrus and its Dependence on Growth Factors and Cytokines

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Introduction

Neurogenesis in the Adult Brain: A Revolution in Neuroscience

Although the idea that neurogenesis occurs in the adult brain was controversial for decades, it has now become well-established (Gross 2000; Eriksson 2003). And as more has become clear about the process of neurogenesis in the adult brain, more of its regulatory mechanisms have also been identified. Indeed, there are many ways that neurogenesis is regulated in the behaving animal normally. In addition, pathological conditions can influence neurogenesis. One of the most robust types of stimuli that increases neurogenesis appears to be seizures. Interestingly, seizures also are remarkable in their ability to change expression of various growth factors, many of which have been causally related to neurogenesis in the normal brain. Therefore, in this chapter, the changes in growth factors that follow seizures, and the potential relationship of these changes in growth factors to seizure-induced neurogenesis will be examined.

Seizure-Induced Neurogenesis in the Dentate Gyrus

Overview

Neurogenesis in the adult brain normally occurs in three areas: the olfactory bulb, subventricular zone, and dentate gyrus of the hippocampus. Neurogenesis in the dentate gyrus is particularly interesting in the context of epilepsy, for several reasons. First, the hippocampus is an area that is particularly susceptible to seizures, and thought to be involved in the etiology of some forms of epilepsy (e.g., temporal lobe epilepsy). Second, the dentate gyrus is thought to play a major role in preventing seizures from invading the hippocampus by acting as a type of gate or barrier (Heinemann et al. 1992; Lothman et al. 1992). Third, the major cell type of the dentate gyrus, the granule cell, is the primary cell type that is born during neurogenesis in the adult dentate gyrus. Finally, the granule cell and its neighbors express many types of growth factors and growth factor receptors, and these change dramatically with seizures (see below). Therefore, it is particularly interesting to attempt to relate the changes in growth factors after seizures to neurogenesis in this part of the brain.

Within the dentate gyrus, progenitors that divide throughout life and become granule cells are found in a 50-100 μm zone just beneath the layer of granule cells (Figure 1). This area is called the subgranular zone (SGZ), and also contains the processes of many adult neurons and glia. It is also richly vascularized, which is important to bear in mind because many of the changes in growth factors, as well as consequences of seizures, may influence the dentate gyrus through this vasculature. The majority of adult neurogenesis in the hippocampus is thought to occur as a result of division of cells that lie within the SGZ. These cells are thought to lie dormant, or stalled within the cell cycle, until they are stimulated to divide, which occurs after seizures. When they do divide, most of them are thought to develop into granule cells and, at least under normal conditions, migrate into the granule cell layer (but see Scharfman et al. 2000).

As mentioned above, seizures greatly increase neurogenesis in the dentate gyrus. This is an extremely robust phenomenon, because many different ways to induce seizures exist, and thus far all appear to increase dentate neurogenesis. Thus, kindling (Parent et al. 1998; Scott et al. 1998; Ferland et al. 2002), electroconvulsive shock (ECS; Scott et al. 2000; Madsen et al. 2003), and status epilepticus, severe, prolonged convulsions, referred to as “status” below; (Parent et al. 1997; Gray and Sundstrom 1998; Covolan et al. 2000; Nakagawa et al. 2000; Scharfman et al. 2000) all increase neurogenesis in the dentate gyrus. Furthermore, seizures do not necessarily need to be severe, because even a single afterdischarge can increase neurogenesis (Bengzon et al. 1997).

Another impressive aspect of seizure-induced neurogenesis is the magnitude of this phenomenon. Thus, the rate of neurogenesis can be increased experimentally in a number of ways, but when seizure-induced neurogenesis has been examined, the increase in numbers of newly-born cells appears to be much greater than the increases that have been observed after other types of manipulations that induce neurogenesis. However, it is difficult to compare different studies because different doses of bromodeoxyuridine (BrdU), the mitotic marker used in most studies, are used. Furthermore, the number of doses and interval between doses can vary between studies. Another important issue is the extent of blood-brain barrier disruption following seizures, because it is conceivable that more BrdU enters the brain from

the periphery when this occurs. Indeed, if the results with BrdU had not been replicated by other markers of newly-born cells that do not involve peripheral injection of a marker, one would have to question the evidence that seizures increase neurogenesis. A related issue is that non-neuronal cells may infiltrate the hippocampus after seizures, so double-labeling with a neuronal marker is critical to determine that the newly-divided cells are neuronal.

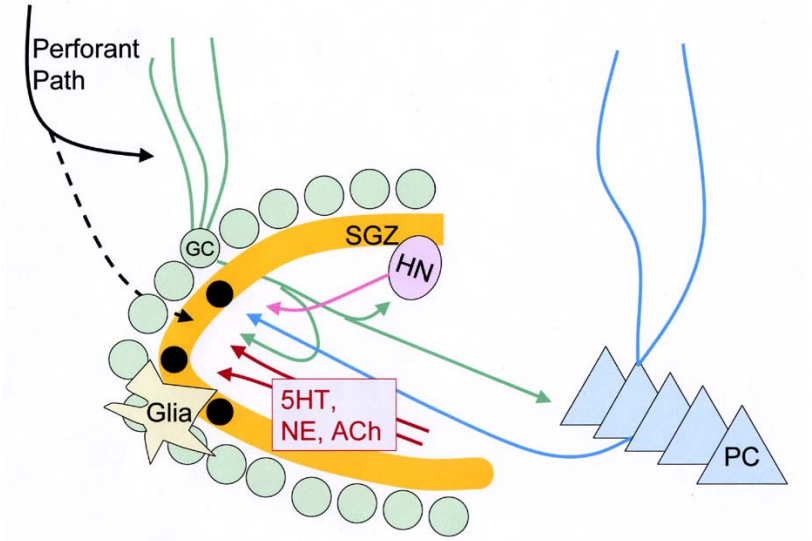

Figure 1. Cells that may influence the precursors in the subgranular zone (SGZ). The illustration shows a cross-section through the dentate gyrus with the cells depicted that could theoretically influence the subgranular zone (SGZ, orange). GC (green) = granule cells. The GCs form a discrete layer of cells (GC layer) adjacent to the SGZ, which contains a variety of "dormant" progenitor cells (black circles) that can divide and become GCs or, potentially, other types of cells (glia, GABA neurons). GC axon collaterals innervate the SGZ as well as hilar neurons and pyramidal cells. HN (pink) = hilar neurons, which include GABAergic interneurons and glutamatergic mossy cells, have somata in the SGZ and outside the SGZ. Their axons and dendrites cross or terminate in the SGZ. PC (blue) = pyramidal cells of area CA3, which have axon collaterals that reach the GC layer, and therefore enter the SGZ. 5HT/NE/ACh (red) fibers innervate the entire hilar region, including the SGZ; 5HT fibers preferentially localized to the SGZ. Glia (light yellow) are located throughout the dentate gyrus, including the SGZ. Perforant path fibers (black) innervate the outer two-thirds of the GC layer and have a smaller projection to the hilus (dotted line). For other description, and references, see text.

Whether Neuronal Activity, Injury, or Growth Factors Trigger Seizure-Induced Neurogenesis

Although often unconsidered, it is not always clear whether the cause of neurogenesis after seizures is the increased neuronal activity, brain injury that is associated with seizures, or something else. One can argue that activity is likely to be at least a contributing factor, because first of all, there is evidence linking hippocampal neuronal activity, be it individual or network activity, to an increase in dentate gyrus neurogenesis. Thus, hippocampal learning (Gould et al. 1999), exercise (which increases brain activity; see chapter by McCloskey and Anderson in this volume) that occurs in conjunction with hippocampal learning (van Praag et al. 1999), stimulation of hippocampal mossy fibers (Derrick et al. 2000) and AMPA receptor activation (Bai et al. 2003) increase neurogenesis, although NMDA receptor antagonists also

increase neurogenesis (Cameron et al. 1998; Bernabeu and Sharp 2000). Second, seizures that lead to very little or no damage, such as kindled seizures, also increase neurogenesis (Parent et al. 1998; Scott et al. 1998; Ferland et al. 2002), although the extent might be less than after more severe seizures associated with neuronal damage. Perhaps seizures and injury both contribute, but do so indirectly. This possibility is based on the fact that both seizures and injury increase neurogenesis and share the ability to induce a similar array of growth factors and peptides (Scharfman 2002), many of which have been suggested to stimulate neurogenesis. This leads one to question whether the increases in growth factors and associated cytokines and peptides are the stimulus for neurogenesis that follows both seizures and injury.

The Time Course of Seizure-Induced Neurogenesis and its Relationship to Changes in Growth Factors after Seizures

Initial studies identified a peak of seizure-induced neurogenesis during approximately the first weeks after pilocarpine-induced status (Parent et al. 1997). In our studies of pilocarpine-induced status, modified to reduce damage and decrease inter-animal variability by anticonvulsant injection at 1 hr after the onset of status (Scharfman et al. 2000; 2001), we found an initial period of primarily non-neuronal proliferation for 1-2 days immediately after status, followed by a switch to neuronal proliferation at approximately days 2-4 that lasted at least 3 weeks. Subsequently, neurogenesis declined to control levels, or even below control levels. All of these studies were based on injection of the mitotic marker BrdU at specific times after status, and immunocytochemistry to identify double-labeled cells using antibodies to BrdU and either neuronal or non-neuronal markers.

This time course provides correlative evidence for the hypothesis that damage initiated by status may trigger an intial invasion of glia and other non-neuronal cells, and perhaps gliogenesis, but that seizure-induced growth factors, which rapidly rise and fall particularly in the first 24 hrs after most seizures (described in more detail below), might be the stimulus that initiates the phase of seizure-induced neurogenesis that begins approximately on day 2-4. The protracted nature of neurogenesis might continue because some of the growth factors remain elevated for long periods of time after status (as further described below).

The eventual decline in neurogenesis in the epileptic animal is particularly interesting given that it resembles what is known about neurogenesis in epileptic patients. Indeed, patients with temporal lobe epilepsy that are medically intractable (seizures unable to be controlled by anticonvulsants) have almost no evidence of increased neurogenesis unless they are younger than 2 years of age (Blümcke et al. 2001). Examination of tissue from intractable patients using markers for young neurons has shown an unusually low number, suggesting neurogenesis is reduced in epileptics (Mathern et al. 2002). Thus, it appears that a history of chronic seizures decreases neurogenesis well below normal levels.

Changes in Growth Factors after Seizures that are Potentially Relevant to Dentate Gyrus Neurogenesis

This section evaluates which growth factors change after seizures and when, in order to evaluate whether they could underlie seizure-induced neurogenesis. Table 1 presents some of the major families of growth factors that are likely to influence the dentate gyrus in the context of seizure-induced neurogenesis, either because they have been shown to modulate neurogenesis, dentate gyrus development in the normal brain, or both. The term "growth factors" will be used loosely to refer to both the growth factors and cytokines of Table I. Of course, there are many more proteins in the body that influence growth and survival of neurons than those listed in Table 1. Many of these other proteins could, in fact, be highly relevant to the present discussion, but their expression and function in the dentate gyrus have not yet been studied even in the normal brain, let alone the epileptic brain.

Of particular interest for neurogenesis in the dentate gyrus are the growth factors that are expressed in the dentate cells or incoming pathways, so that they are in an appropriate spatial location to regulate cells of the SGZ (Figure 1). The list of cells and fibers that exist within the SGZ, and therefore are in a position to influence precursors, is actually not that long (for more information about cell types in the dentate gyrus, see Scharfman 1992, 1999). The primary cell type of the dentate gyrus, the granule cell, has axon collaterals that innervate the SGZ, as well as the proximal dendrites of area CA3 pyramidal cells. There are also many types of GABAergic interneurons that either have cell bodies in the SGZ, or have dendrites and axons that pass into that layer. The glutamatergic mossy cells, which have their somata in the hilus, have dendrites and axon collaterals that reach the SGZ, although their major projection is to the inner molecular layer. Glia are dispersed throughout the dentate gyrus, and should not be excluded from the list of cells that potentially influence the SGZ.

In addition to the cells within the dentate gyrus, incoming afferents are also important to consider. The major afferent input to the dentate gyrus is from layer II neurons of the entorhinal cortex, and they are thought to innervate the outer two-thirds of the molecular layer. This projection pattern would place these cortical neurons in a position to only indirectly modulate the SGZ, probably by their influence on granule cells or nonprincipal cells. However, there may be some projections of deep layer entorhinal cells or other neurons of the entorhinal cortex to the SGZ (Kohler 1985; Deller et al. 1996).

Other afferents to the hilus which could possibly influence newly generated cells arise from serotonergic or noradrenergic ascending systems that terminate in the hilus (Swanson et al. 1987). However, very little information is available about the changes in noradrenergic and serotonergic input to the hilus after seizures, and therefore these systems will not be included in the subsequent discussion. It is currently unknown if these monoaminergic fibers are rapidly depleted of amines after a seizure, or whether they could rapidly increase their stores and then have greater effects during the first days after status. Further, it is unknown whether noradrenergic and serotonergic receptors change after seizures. This lack of information is unfortunate because, particularly for serotonin, dentate gyrus neurogenesis is thought to be highly influenced by serotonin (Gould 1999). In fact, it has been proposed that

seizure-induced neurogenesis is mediated entirely by 5HT1A receptors (Radley and Jacobs 2003). Certainly this theory is consistent with the neuroanatomical information showing that the plexus of serotonergic fibers innervating the dentate gyrus targets the subgranular zone relatively specifically (Swanson et al. 1987). Norepinephrine is also thought to influence dentate gyrus neurogenesis, but less is known about its role. However, one study has identified that it may selectively enhance proliferation (Kulkarni et al. 2002).

In addition to inputs from the brainstem, septal cholinergic fibers form a major projection to hilar neurons, both the GABAergic cells as well as the mossy cells (Leranth and Frotscher 1987; Deller et al. 1999). Although the densest cholinergic fiber plexus in the dentate gyrus is in the supragranular region, rather than the hilus, there still are a substantial number of fibers present in the hilus (Matthews et al. 1987; Nyakas et al. 1987) that could infiltrate the SGZ. These projections are important because there appears to be an influence of α7 nicotinic receptors on proliferation in the dentate gyrus (Koike et al. 2004), and nicotinic receptors of this class are clearly present in the hilus (Swanson et al. 1987). Furthermore, acetylcholine appears to influence the division of cortical precursors (Ma et al. 2000).

The Neurotrophin Family

One of the family of proteins that has been associated most closely with the growth and survival of neurons is the neurotrophins. The first members of this family to be identified were nerve-growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3). These proteins bind, respectively, to the tyrosine kinase receptors trkA, trkB and trkC. NT-3 is exceptional because it can bind to more than one trk, but it binds with highest affinity to trkC. In addition, neurotrophin-4/5 (NT-4/5) is a member of this family, and is thought to bind to trkB. A neurotrophin-6 (NT-6) also exists, but it has thus far only been identified in fish. All neurotrophins bind to the p75 receptor, originally identified as the low affinity nerve growth factor receptor (LNGFR).

In normal hippocampus, expression of NGF, BDNF, and NT-3 occur in many areas. Historically, NGF protein has been associated with cholinergic innervation of the hippocampus (Kordower et al. 1988), although results using different antibodies have indicated that granule cell mossy fibers may also contain NGF (Conner et al. 1992). Indeed, granule cells and pyramidal cells make NGF mRNA (Bandtlow et al. 1990). BDNF mRNA appears to be expressed similarly throughout the hippocampal cell layers, but BDNF protein is in highest concentration in granule cells (Conner et al. 1997; Yan et al. 1997). NT-3 mRNA (Phillips et al. 1990) and protein (Zhou and Rush 1994) have been localized to granule cells and pyramidal cells, and the same appears to be true for NT-4/5 (Friedman et al. 1998). However, NT-3 protein appears to be preferentially localized to CA2, whereas NT-4/5 immunoreactivity is greatest in the CA3 cell layer (Friedman et al. 1998). Some studies have also suggested that neurotrophins can be synthesized in GABAergic neurons (Rocamora et al. 1996; Pascual et al. 1999).

NGF

A dramatic increase in dentate granule cell NGF mRNA was first identified by Gall and coworkers after intracerebroventricular injection of kainic acid (Gall and Isackson 1989; Isackson et al. 1991). There also were increases in the superficial entorhinal cortical cells, implicating a possible change in the cells of origin of the perforant path that could influence the dentate gyrus (see above and Figure 1). The increase peaked between 15 and 24 hrs after the onset of seizures, and had returned to control values by 24 hrs after drug administration. Subsequent studies showed similar effects after other methods to induce seizures, such as hilar lesions, but with a slightly more protracted time course (lasting up to 96 hrs; see Gall et al. 1991 for review). The convulsant pentylenetetrazol (Humpel et al. 1993), kindling (Ernfors et al. 1991; Bengzon et al. 1992), angular bundle stimulation (Springer et al. 1994), and ethacrynic acid-induced seizures (Suzukawa et al. 1999) all increased dentate granule cell NGF mRNA. Thus, regardless of the length of seizures, severity of seizures, or method of seizure induction, growth factor induction was extremely robust. This theme continued as more growth factors were examined after seizures (see below).

BDNF

Shortly after the demonstration that NGF mRNA increased in dentate granule cells after seizures, a very similar temporal and spatial pattern of changes was shown for BDNF mRNA. Isaakson et al. (Isackson et al. 1991) showed that hilar lesion-induced recurrent seizures led to increased BDNF mRNA. The sensitivity to this effect was remarkable: only one epileptiform afterdischarge was required to increase BDNF mRNA in granule cells, suggesting that BDNF may in fact be one of the growth factors most sensitive to changes in neural activity. Indeed, granule cell BDNF mRNA could be induced by trains of stimuli to the perforant path (Springer et al. 1994) or stimuli that elicit LTP (Patterson et al. 1992; Castren et al. 1993; Bramham et al. 1996; Morimoto et al. 1998), which did not involve seizures. Other studies also showed that the seizure-induced change in granule cell BDNF mRNA was rapid and robust in granule cells (kainic acid: Dugich-Djordjevic et al. 1992; hilar lesions: Rocamora et al. 1992).

It was shown in some of these studies that the high affinity receptor for BDNF, trkB, also increased message transiently after kainic acid treatment (Dugich-Djordjevic et al. 1995), although a different study of kainic acid-induced seizures showed that the most robust increase was actually not in the full length form of trkB, but in the truncated form of trkB (Rudge et al. 1998; see also Simonato et al. 2002). This truncated form is likely to subserve distinct functions given that it lacks the cytoplasmic kinase domain of the full-length receptor. After fluorothyl-kindling, neither full-length nor truncated trkB appeared to change, although there was an increase in BDNF (Mhyre and Applegate 2003). After ECS, both truncated and full-length trkB changed, but appeared to do so with distinct time courses: the increase in truncated trkB occurred at a similar time as the increase in BDNF mRNA, but the increase in full-length trkB occurred subsequently, after a delay of a few hours (Lindefors et al. 1995).

As antibodies to BDNF improved, the studies of message were replicated to determine when and where BDNF protein increased. Not surprisingly, it was demonstrated that BDNF protein increased in granule cells after seizures, and the peak in protein expression occurred after the maximal elevation in mRNA. After kainic acid-induced seizures, Rudge and colleagues reported a maximum at 24 hrs (Rudge et al. 1998). But the elevated protein levels appeared to last long after 24 hrs, because immunocytochemical studies showed that BDNF protein was elevated long after status, induced either electrically (Vezzani et al. 1999b) or with pilocarpine (Scharfman et al. 1999; 2002b). In our studies of animals that have had pilocarpine-induced status, BDNF protein is elevated in the mossy fibers and hippocampal neuropil for at least the subsequent 13 months, which is as long as we have looked thus far (see Scharfman et al. 1999). It is important to point out that it is unclear in the latter studies (Scharfman et al. 1999; Vezzani et al. 1999b) just how much the long-lasting elevation is due to the initial period of status, because the animals begin to have recurrent spontaneous seizures in the weeks following status, and continue intermittently thereafter. It is conceivable that after each spontaneous seizure, BDNF rises, and the seizures are frequent enough to prevent BDNF from ever decaying to normal levels. Mhyre and Applegate (2003), using the fluorothyl kindling model of epilepsy, found that the elevation in BDNF lasted as long as they chose to examine (29 days), yet their animals were not having spontaneous seizures. The results of studies in rats are similar to the results of studies of human epilepsy, which have demonstrated that granule cell BDNF mRNA (Mathern et al. 1997; Murray et al. 2000) and protein (Takahashi et al. 1999) are elevated in medically-intractable cases.

NT-3 and NT-4/5

In contrast to the robust increases in NGF and BDNF, NT-3 *decreases* after seizures (pilocarpine, Schmidt-Kastner and Olson 1995; kainic acid, Dugich et al. 1995; Katoh-Semba et al. 1999; hilar lesion, Rocamora et al. 1992; quinolinic acid, Rocamora et al. 1994) and NT-4/5 does not appear to change (Katoh-Semba et al. 2003). The decrease in NT-3 demonstrates an important exception to the rule that growth factors in granule cells increase after seizures. Thus, the changes in all of the growth factors are probably more important to consider than any single change in isolation.

Although NT-3 itself appears to decrease in all studies to date, changes in trkC have been less consistent (Bengzon et al. 1993; Merlio et al. 1993; Mudo et al. 1995). The mixed results regarding trkC receptors will be important to clarify because, if they increase, as indicated by one study (Mudo et al. 1995), a decline in NT-3 levels might be compensated by more receptors. This finding raises an important point: one needs to understand not just the changes in growth factor levels, but also the changes in their receptors, before predicting how the altered levels might influence function. Indeed, much more information is needed, exemplified by the fact that very little is known about many growth factors that could potentially change in the dentate gyrus after seizures.

The Fibroblast Growth Factor (FGF) Family

Studies of the family of fibroblast growth factors (FGFs), which include 22 known subtypes in man and 23 in rat, initially focused on their ability to influence the growth of fibroblasts, but the functions were later expanded when it was demonstrated that these proteins also influence the proliferation of many other cell types (Burgess and Maciag 1989). For example, basic FGF (bFGF, also called FGF-2, EDGF, or HBGF-2) can influence the differentiation and migration of neurons and glia (Baird et al. 1986).

In both immature and mature hippocampus, aFGF is normally expressed only at low levels. However, in the adult rat, bFGF is detected in numerous astrocytes and in area CA2 neuronal somata (Eckenstein et al. 1994; Williams et al. 1996). FGF receptor type 1 (FGFR-1 or "flg") is normally present on hippocampal pyramidal cells in man, although these receptors and other FGF receptors are thought to exist primarily on glia (El-Husseini et al. 1994; Gonzalez et al. 1995; Ferrer and Marti 1998; Takami et al. 1998).

To date, studies of FGF in hippocampus after seizures have been restricted to the aFGF (acidic FGF, also called FGF-1, ECGF, or HBGF-1) and bFGF. Both aFGF and bFGF mRNA and protein appear to increase after seizures, using a variety of protocols for seizure induction, such as injection of bicuculline in area tempestas (Riva et al. 1992) or more common methods, such as ECS (Follesa et al. 1994), hilar-evoked seizures (Gall et al. 1994), or kainic acid (Bugra et al. 1994; Riva et al. 1994; Van Der Wal et al. 1994). After hilar lesions, bFGF increases in dentate granule cells and cortical neurons, including superficial layers of the entorhinal cortex, but this elevation is transient (12-24 hrs; Gall et al. 1994). Otherwise, most of the increases appear to be in glia. After entorhinal cortical lesions, bFGF increased in the dentate gyrus molecular layer, primarily in glia located in the terminal zone of the perforant path (Gomez-Pinilla et al. 1992). This result is interesting because damage after seizures often occurs in the entorhinal cortex, and may stimulate some of the same changes. After kindling, the elevation in FGF was more selective. Thus, Simonato and colleagues (Simonato et al. 1998) found that bFGF could be induced in hippocampus by a kindled seizure, but not aFGF. Sato et al (Sato et al. 1996) did not find an elevation in either aFGF or bFGF after amygdala kindling.

Regarding FGF receptors, Van Der Wal and colleagues showed that FGFR-1 protein developed in the molecular layer after kainic acid-induced seizures, and by 24 hrs had spread throughout hippocampal and cortical lamina, mostly in astrocytes (Van Der Wal et al. 1994). Bugra and colleagues also showed that FGFR-1 increased, again after kainic-acid treatment, but they found that the receptors were induced within the major cell layers (Bugra et al. 1994).

The Epidermal Growth Factor (EGF) Family

Epidermal growth factor (EGF) was first identified as a peptide that helped epithelial tissues heal and repair. However, in addition to wound healing, it is a significant mitogen, important in embryogenesis, cell growth and differentiation. In hippocampus, mRNA for EGF and its relative heparin-binding growth factor (HB-EGF), is primarily expressed in

pyramidal cells (Lazar and Blum 1992; Tucker et al. 1993; Mishima et al. 1996). EGFR mRNA is also expressed in pyramidal cells, primarily in area CA2 (Tucker et al. 1993).

Members of the EGF family appear to increase after seizures, although there are no studies to date that have looked at expression of EGF itself. However, HB-EGF mRNA increases in both the cell layers of the dentate gyrus and molecular layers following kainic acid treatment, with a peak at 24 hr (Opanashuk et al. 1999). Another member of this family, Neuregulin, increased in hippocampus after kainic acid treatment (Eilam et al. 1998). In addition, some of the ErbB receptors, which mediate effects of the EGF family, appear to be influenced by seizures. Hippocampal ErbB4 increased after kainic acid treatment in a similar fashion as Neuregulin, without a change in ErbB3 (Eilam et al. 1998). Currently there is little information available for ErbB1 or ErbB2, the other receptors of this class.

The Insulin-Like Growth Factor (IGF) Family

Originally identified as a mediator of the effects of growth hormone, current views of insulin-like growth factor 1 (IGF-1, also called somatomedin C) have expanded, as it has been shown to be critical to the growth and differentiation of neurons. In hippocampus, IGF-1 has been localized to glia in immature brain, but in adults, immunoreactivity shows expression of IGF-1, IGF-1 binding, and IGF receptor type I (IGFR-I) expression in hippocampal neurons, not glia (Bohannon et al. 1988; Unger et al. 1989; Werther et al. 1990). IGF-2 is not present in the adult hippocampus, but IGFR-II (also termed the mannose 6-phosphate receptor) is expressed throughout the hippocampal cell layers of the adult; again, no presence in glia has been noted in the adult brain (Couce et al. 1992; Hawkes and Kar 2003).

The activity of the IGF family may be distinct from other growth factors because binding for IGFR-I and IGFR-II appear to decrease in all studies of seizures that have been conducted to date. Thus, after kainic acid, IGFR-I, IGFR-II, and insulin receptor binding decreased in hippocampus (Kar et al. 1997). IGFR-I binding changed in ways that could be relevant to neurogenesis, because the only change was in the hilus, the location of the SGZ, and it stayed decreased for a long time (30 days). In contrast, IGFR-II binding declined only in the pyramidal cell layers (Kar et al. 1997). Insulin receptor sites decreased in the molecular layer and area CA1 (Kar et al. 1997). After amygdala kindling, there was also a decrease in IGFR-I binding, but no change in IGFR-II or insulin receptor binding (Kalynchuk et al. 2002). Expression of IGF itself has not been examined after seizures to date.

Vascular-Endothelial Growth Factor (VEGF)

Studies of VEGF originated in the periphery, where the robust actions of VEGF to permeabilize endothelium created great interest. This interest was followed by even more attention when the angiogenic actions of VEGF were identified (see chapter in this volume by Susan Croll and colleagues). More recently, VEGF has been implicated in CNS function. In the normal brain, VEGF protein appears to be primarily associated with astrocytes, with

receptors on both neurons and glia, but no normal expression in granule cells or pyramidal cells. However, mRNA for VEGF and two of its receptors, VEGFR1 and VEGFR2, appears to be in granule cells and pyramidal cells, at least in the C57bl/6 mouse hippocampus (Marti 2002).

Very few studies have examined VEGF after seizures. In the initial 24 hrs after pilocarpine-induced status epilepticus, VEGF immunocytochemistry showed increased punctate immunoreactivity along processes of cells that appear to be astrocytes, suggesting that there is an increase in bound VEGF on astrocytes (Croll et al. 2004). In addition, hippocampal pyramidal cells appeared to make VEGF protein in the first 24 hrs after status (Croll et al. 2004). However, this increase in expression declined within 3 days, and in animals with spontaneous recurrent seizures, VEGF expression in neurons is not apparent (Croll et al. 2004). Instead, VEGF protein that is associated with glial processes is increased, and in some animals with chronic seizures, this increased level of glial-associated VEGF is much greater than the levels detected in animals that are examined 24 hrs after status. Other models of seizures, using ECS, have shown an upregulation of VEGF mRNA expression (Newton et al. 2003). After other types of insults, such as ischemia, VEGF mRNA has been shown to be transiently expressed in hippocampal pyramidal cells (Lee et al. 1999; Chodobski et al. 2003).

The Transforming Growth Factor β (TGFβ) Superfamily

TGFβ

TGFβ exerts a variety of effects on physiological, immune, and growth-related processes. In rat, TGFβ exists in hippocampal cell layers in the normal hippocampus (Kim et al. 2002), especially in area CA1 pyramidal cells (Zhu et al. 2000). After seizures, several changes in expression occur. In the kainic acid model, there are reports of an initial decrease in TGFβ type3 (TGFβ-3) mRNA in the first hours after kainic acid-induced seizures, but the protein was elevated for up to 30 days in area CA1 (Kim et al. 2002). Other reports indicate a persistent increase in TGFβ in glia for 3 weeks after electrically-induced status (Aronica et al. 2000). A delayed and long-lasting increase in TGFβ in glia is associated with injury (Hughes et al. 1999), and indeed the increase in TGFβ–1 mRNA after kainic acid has been found in areas where neuronal damage occurs (Morgan et al. 1993). However, TGFβ has been found to increase acutely in hippocampus of amygdala-kindled rats, which have a hippocampus thought to be almost devoid of damage (Plata-Salaman et al. 2000), so damage is unlikely to be the only stimulus that elevates TGFβ expression.

The Glia-Derived Neurotrophic Factor (GDNF) Family

GDNF

GDNF is known for the ability to promote neuronal survival, particularly the survival of dopaminergic neurons and motoneurons. However, GDNF is also expressed elsewhere, and may have relevance to diseases besides those that involve dopaminergic neurons and motoneurons. The actions of GDNF are mediated by tyrosine phosphorylation of the proto-oncogene c-Ret, in combination with a GDNF-binding protein, termed GDNF receptorα (GFRα), which has 4 known variants (GFRα 1, 2, 3, 4). In hippocampus, GDNF and c-Ret are normally expressed at low levels, although GFRα is strongly expressed throughout the neuronal cell layers (Humpel et al. 1994; Trupp et al. 1997), suggesting that c-Ret-independent actions may occur.

There is a great deal of evidence that GDNF and its receptors change after seizures (see chapter in this volume by Merab Kokaia and Olle Lindvall). Initial studies, focusing on GDNF mRNA, identified a rapid increase in granule cells after pilocarpine (Schmidt-Kastner et al. 1994) or kainic acid-induced seizures (Humpel et al. 1994). Within 2 hrs after the onset of seizures, there was already a large increase, and this abated within 24 hrs. GDNF mRNA was also increased in the hilus and pyramidal cell layers, although this occurred with more of a delay and remained elevated at 24 hrs (Humpel et al. 1994). A subsequent study of kainic acid-induced seizures also observed an initial rise in granule cells, followed by increased GDNF mRNA in the hilus and CA3 region (Trupp et al. 1997).

Additional studies using rapidly recurring hippocampal seizures, rather than status epilepticus, also showed elevated GDNF mRNA in granule cells by 2 hrs (Kokaia et al. 1999). In this study, the elevation was specific to granule cells and for 1 week. The relative of GDNF, Neurturin, also increased in granule cells, although the time course was slower, reaching a peak by 24 hrs and returning to baseline values by 1 week (Kokaia et al. 1999). In C57bl/6 mice, a similar pattern was found using a similar paradigm to elicit seizures (Nanobashvili et al. 2003). In contrast to the types of seizures described above, no change in GDNF mRNA was detected in hippocampus after acute or chronic ECS (1 ECS daily for 10 days; Chen et al. 2001).

In contrast to the studies above, which examined mRNA, Mikuni et al. (Mikuni et al. 1999) showed that GDNF protein increased as well as message. In their studies, a unilateral injection of kainic acid increased GDNF protein in granule cells within 3 hrs, and this continued for 4 days, returning to control values by 7 days (Mikuni et al. 1999).

How the different receptor components for GDNF change after seizures is complex. After kainic acid treatment, c-Ret mRNA increased in non-pyramidal cells for approximately 24 hrs, and GFR mRNA increased in granule and hilar cells (Trupp et al. 1997; Reeben et al. 1998). After acute and chronic ECS, there was no change in c-Ret mRNA, but GFRα1 and GFRα2 mRNAs increased for approximately 24 hrs in granule cells (Chen et al. 2001). After rapidly recurring hippocampal seizures, either in mouse or rat, c-Ret increased in the hilus and CA3 by 6 hrs, returning to baseline values by 1 week. GFRα1 increased in many areas,

including the granule cells, hilus, and CA3, but with a more protracted time course, peaking at about 24 hrs. Values return to control levels by 1 week. In contrast to the increases observed in GFRα1, GFRα2 mRNA declined. The decline was confined to CA1 in the rat, but in the mouse, it declined in both granule cells and pyramidal cells. Interestingly, at 1 week, there was an elevation in GFRα2 in the CA1 and CA3 cells (Kokaia et al. 1999; Nanobashvili et al. 2003).

Other TGFβ Family Members

There is not a great deal of information available about the potential changes in the other members of the TGFβ family with seizures, even though they could be highly relevant to the development and maturation of new cells in the dentate gyrus. For example, bone morphogenic proteins (BMPs) in general are critical to development. BMP-4 appears to suppress glial fate, and may therefore permit neuronal differentiation of progenitors that have just divided after seizures (Charytoniuk et al. 2000). Although there is some discrepancy in the current literature, there are data to suggest that the hippocampus normally expresses BMP-2,4,5,6, and 7 (Chen et al. 2003; Fan et al. 2003; but see Charytoniuk et al. 2000). Although many BMPs decrease expression in the adult brain, BMP-6 remains expressed in the adult, and one of the few places in the brain it remains is hippocampus (Tomizawa et al. 1995), suggesting its importance to hippocampal function in the mature brain. In addition, the relatives of BMPs, growth/differentiation factors (GDFs), particularly GDF1 and 10, have been localized to neurons of hippocampus (Soderstrom and Ebendal 1999). Osteogenic proteins 1 and 2 (OPs), other members of the TGFβ superfamily, do not appear to be expressed in hippocampus (Soderstrom and Ebendal 1999).

The BMPs have several receptors: BMPR IA, IB, and II. These also potentially interact with receptors for Activin (ActRI and II). BMPR II and the ActRI receptors are in the hippocampus of the adult brain, but BMPR I is not (Soderstrom et al. 1996). Although no evidence to date has identified changes in BMPs, their relatives, or their receptors after seizures, BMPR II mRNA increases after transient global ischemia (Charytoniuk et al. 2000), and a rapid rise in granule cells occurs after mild contusion injury (Lewen et al. 1997).

Cytokines

The Interleukins (ILs)

The interleukin family includes more than 18 proteins that stimulate the immune system in various ways. They are generally secreted from leukocytes, hence the suffix “-leukin” (see Vezzani et al. 2004, for review). Several members of this family dramatically rise after seizures, and do so in hippocampus. These cytokines are highly relevant to the present discussion because inflammation and interleukins have recently been shown to regulate dentate gyrus neurogenesis (Ekdahl et al. 2003; Monje et al. 2003).

After electrically-induced status epilepticus, IL-1β, IL-1 receptor antagonist (an endogenous antagonist of the IL-1 receptor) and IL-6 increased within 2 hrs in both microglia and astrocytes (DeSimoni et al. 2000). This effect was transient, except for IL-1β, which remained elevated in hilar interneurons and CA3 cells for at least 60 days after status (Vezzani et al. 1999a; DeSimoni et al. 2000). Focal injection of kainic acid into hippocampus also led to an increase in glial IL-1β, and this was higher in animals with seizure-induced damage than those treated with focal bicuculline, which does not lead to cell loss (Vezzani et al. 1999a). These studies all examined protein levels, using methods such as immunocytochemistry and ELISA.

After lithium-pilocarpine treatment, which is another method to induce status that is slightly different from pilocarpine treatment alone, there was a rapid increase of IL-6 and IL-11 in nonprincipal cells of hippocampus. This was followed by a modest elevation in receptors for IL-6 and IL-11 (Rosell et al. 2003).

After amygdala kindling, there was an elevation in mRNA for IL-1β, and IL-1RI in hippocampus, but this was apparent shortly after the last kindled seizure and not 3 weeks later, indicating a transient effect (Plata-Salaman et al. 2000). This study exemplifies a general theme that is also apparent from some of the other studies described above, that the more severe seizures (i.e., status) often led to longer-lasting changes than single seizures and kindled seizures. It is hard to know, however, if this profile is due to the increase in neuronal injury that accompanies more severe seizures, or whether it can be attributed to the greater level of activity.

Tumor Necrosis Factorα (TNFα)

TNFα is best known for its diverse pro-inflammatory actions. However, it may also have other actions: interestingly, it has been shown to regulate norepinephrine release (Ignatowski et al. 1997). Although no studies have been conducted along these lines in hippocampus, it is tempting to speculate that TNFα in the dentate gyrus could regulate the influence of amines on neurogenesis (see above). This would not be likely in the normal brain, because there is little expression of TNFα under normal conditions in adult hippocampus (Tchelingerian et al. 1994). However, a transient increase in TNFα protein was detected in glia within 2 hrs of status, which lasted 24 hrs. No long-lasting changes were detected (Vezzani et al. 2004).

After amygdala kindling, TNFα was elevated in hippocampus, but only when examined 2 hrs after the last seizure. Like the changes in IL-1β after amygdala kindling, TNFα levels were similar to controls when examined 3 weeks after the last seizure (Plata-Salaman et al. 2000).

Leukemia Inhibitory Factor (LIF or CDF; Cholinergic Differentiation Factor)

LIF has multiple actions that include an influence, as the name suggests, on leukemic cells, but LIF also acts on embyronic stem cells (Williams et al. 1988; Gearing 1993), making it more relevant to the present discussion. In addition, LIF mRNA is expressed in normal rat

hippocampus, where it appears to be localized to neuronal cell layers, particularly area CA3 (Yamakuni et al. 1996). After kainic acid-induced seizures, LIF mRNA increased in hippocampus greatly, peaking between 8 and 24 hrs after kainic acid administration (Minami et al. 2002). The first site where LIF increased was the granule cell layer, followed by the hilus and finally the pyramidal cell layer. The changes were transient, so that by the time the pyramidal cell layers demonstrated changes, the elevation in the granule cell layer had already subsided. After pilocarpine-induced status, increased LIF mRNA was also reported, but mostly in GFAP-positive astrocytes, and the distribution was evenly dispersed throughout the hippocampus. This increase occurred within 1 hr, and subsided by 3 days (Jankowsky and Patterson 1999). Using lithium-pilocarpine to induce status, LIF mRNA was shown to rapidly increase in granule cells and nonprincipal cells, followed by a modest and slow elevation in LIF receptor (Rosell et al. 2003).

Ciliary Neurotrophic Factor (CNTF) and Oncostatin-M (OSM)

CNTF and its receptor, CNTFRα, are expressed in glia of hippocampus under normal conditions (Dallner et al. 2002). CNTF has diverse potential, because it has been linked to neurogenesis and neuroprotection in hippocampus (discussed further below).

After pilocarpine-induced seizures, CNTF mRNA increased in glia, with a similar distribution but slower time course than LIF. OSM mRNA, a relative of LIF and CNTF, also increased. CNTF mRNA levels remained elevated for at least 1 week after status (Jankowsky and Patterson 1999). However, after lithium-pilocarpine, no elevation in either CNTF or OSM were detected consistently, although some modest increases occurred in some animals (Rosell et al. 2003).

Summary

The changes in growth factors within the hippocampus after seizures are remarkable. These changes are some of the most striking that have been described in the field of neural plasticity. And it is important to recognize that this list of changes may only be a fraction of what actually occurs, because there are a number of growth factors known to influence, for example, neural progenitors (e.g. various interleukins, not listed in Tables 1-3), and they have not even been examined as yet.

There are a few general themes that are apparent in the data described above. First, most changes that occur after seizures are usually short-lived, peaking within hours and lasting usually no more than 24 hrs. What that suggests is that the primary influence is likely to be on proliferation rather than other, later developmental phases of newly-born cells, which occur as they differentiate, form synapses, etc. But there are some notable exceptions (Table 2 and Figure 2). Importantly, some of the studies have only focused on mRNA and short-durations of time after seizures. These studies of course can not tell us how long the protein that is made from elevated mRNA will endure, so it may be that Table 2 and Figure 2

underestimate the persistence of growth factors that could remain altered for long periods of time after seizures.

Another generality is that the more severe the seizure, the more striking is the change after seizures. Thus, the most robust changes appear to occur after status relative to a single seizure, or kindled seizures. There is also more agreement among studies of status than studies that have examined milder forms of seizures. The consistency in changes after status are apparent even if status is induced by distinct methods. It is actually surprising that the different studies of status are in such agreement given that some use convulsants (pilocarpine, kainic acid) and others use electrical stimulation, and some truncate status by anticonvulsant administration after 1 hr whereas, in other studies, status continues for up to 5 hrs. Anecdotally, this provides some evidence against the argument that damage is the primary stimulus, rather than the seizures, in growth factor induction, because the degree of damage after 8 hrs of status is much more severe than 1 hr. It may be that even 1 hr of status is such a severe event that its additional consequences, if prolonged beyond 1 hr, are relatively inconsequential to growth factor induction. It is also the case that anticonvulsant treatment at 1 hr after the onset of status does not entirely stop seizures, so the distinctions may not be as great. Thus, it may not be a distinction between 1 vs. 8 hrs of status, but actually be more along the lines of 1 hr status plus up to 5 hrs thereafter of mild seizures, vs. 3-5 hrs of status plus 1-3 hrs of subsequent intermittent seizures.

Regardless, even though the reason is unclear, findings are in much greater agreement for seizures that involve a period of status than other models of epilepsy such as kindling or ECS. Table 1 and Figure 2 summarize growth factor changes after status only. Clearly the greatest changes are in the first 24 hrs after seizures, shown in Figure 2A. In Figure 2B, the changes that have not subsided even after a few days are shown. As mentioned above, this is important because the latter will be able to influence a variety of processes relevant to newly-born cells beyond the initial cell division in the SGZ. How this is likely to unfold is described further below.

How Do Growth Factors Influence Seizure-Induced Neurogenesis?

Although the initial rise in many of the growth factors after seizures could conceivably trigger seizure-induced neurogenesis, to what extent growth factors are completely responsible for this phenomenon, and whether other aspects of new cell development are also modulated by changes in growth factors after seizures, is hard to predict. This is due to the fact that the influence of these proteins on the rate of precursor division, differentiation into neurons, migration and outgrowth have not been completely clarified, even in the normal brain. However, a few predictions can be made given what is known. The predictions are based on the assumption that growth factor function in the normal brain or during development will be similar to growth factor function after seizures, which is admittedly a major assumption.

The Influence of Growth Factors on Neurogenesis

Most studies that discuss an influence on dentate gyrus neurogenesis have focused on the rate of precursor division, reflected in BrdU incorporation of cells in the SGZ that have divided as a result of the stimulus of seizures. This first step in neurogenesis is actually proliferation, although sometimes the studies make this difficult to interpret because animals are sacrificed quite some time (days) after BrdU incorporation, and then the study is actually looking not only at proliferation but short-term survival as well. Of course proliferation itself is not necessarily simple. For example, an increase in the rate of neurogenesis could occur because of a stimulus that takes a precursor cell lying in a dormant state and makes it enter the cell cycle. Or, one can take the point of view that all cells in the SGZ are really in a protracted cell cycle already, and the stimulus of seizures merely shortens the phases so that the cell rapidly enters mitosis. There also could be a transformation of a dormant cell into a precursor before it can divide.

Theoretically, many candidate growth factors could mediate these processes. Indeed, of the changes that are listed in Table 2, most of the growth factors that increase after seizures are also ones that increase the rate of neurogenesis in the normal brain. This supports the argument that, potentially, seizure-induced neurogenesis is initiated entirely by the upregulation of growth factors by seizures. Examples of growth factors known to increase the rate of neurogenesis in normal brain include BDNF (Pencea et al. 2001; Katoh-Semba et al. 2002; Lee et al. 2002), IGF-1 and TGFα (Cameron et al. 1998), TGFβ (Mahanthappa and Schwarting 1993)**,** and LIF (Satoh and Yoshida 1997). Factors that have specifically been shown to increase *dentate gyrus* neurogenesis include VEGF (Jin et al. 2002), bFGF (Cheng et al. 2002), CNTF (Emsley and Hagg 2003), and HB-EGF (Jin et al. 2003).

However, there are some growth factor changes after seizures that one would expect to decrease neurogenesis. For example, IGFR-I and IGFR-II binding decreases after status, but IGF-1 is a potent inducer of neurogenesis in the normal brain (Lichtenwalner et al. 2001; Anderson et al. 2002). Thus, seizures should decrease the ability of IGF to increase neurogenesis.

Another complication is that inflammation has been shown to inhibit neurogenesis (Ekdahl et al. 2003), and this is likely to be mediated by the pro-inflammatory interleukins (Monje et al. 2003). Interleukin-6 is a prime candidate (Vallieres et al. 2002). Given that the interleukins which mediate inflammation, such as the interleukins IL-1β and IL-6, increase after seizures (see above), a decline in neurogenesis after seizures might be expected as a consequence. Indeed, the increase in IL-1β lasts for quite a long time (Vezzani et al. 2002; Vezzani et al. 2004), which would be likely to act as a long-lasting negative influence on neurogenesis.

Table 1. Growth Factor and Cytokine Families

TYROSINE KINASES Family	Abbreviation	Receptors
The Neurotrophin family		
Nerve growth factor	NGF	trkA
Brain-derived neurotrophic factor	BDNF	trkB
Neurotrophin-3	NT-3	trkC
Neurotrophin-4/5	NT-4/5	p75
The Fibroblast Growth Factor family (FGF 1-23)		
Fibroblast growth factor 1(acidic)	aFGF, FGF1	FGFR I (flg)
Fibroblast growth factor 2 (basic)	bFGF, FGF2	FGFR III FGFR III FGFR IV
The Epidermal Growth Factor family		
Epidermal growth factor	EGF	EGFR I (erbB1)
Heparin-binding epidermal growth factor	HB-EGF	EGFR II (erbB2)
Transforming growth factor α	TGFα	EGFR III (erbB3)
Neuregulins 1-3		EGFR IV (erbB4)
The Insulin Growth Factor family		
Insulin	Ins	IR
Insulin-like growth factor 1	IGF-1	IGFR I
Insulin-like growth factor 2	IGF-2	IGFR II (M6P)
Vascular Endothelial Growth Factor		
Vascular endothelial growth factor	VEGF, VEGF (A) VEGF(B) VEGF(C) VEGF (D) VEGF (E)	VEGFR 1 (flt 1) VEGFR 2 (flk 1) VEGFR 3 (flt 4) neuropilin 1 neuropilin 2
Placental growth factor	PlGF	

SERINE THREONINE KINASES Family	Abbreviation	Receptors
The Transforming Growth Factor superfamily		
Transforming growth factor β		
Transforming growth factor β1	TGFβ1	TGFβ I
Transforming growth factor β2	TGFβ2	TGFβ II
Transforming growth factor β3	TGFβ3	TGFβ III
Glia-derived neurotrophic factor family		
Glia-derived neurotrophic factor	GDNF	c-Ret and GFRα1
Neurturin		c-Ret and GFRα2
Artemin		c-Ret and GFRα3
Persephin		
Bone-morphogenic proteins (BMP 1-20)		
Bone-morphogenic proteins	BMPs	BMPR IA BMPR IB BMPR II
Growth/differentiation factors (GDF 1-10)		
Growth/differentiation factors	GDFs	
Activin/Inhibin		Act R I Act R II

CYTOKINES Family	Abbreviation	Receptors
Tumor Necrosis Factor superfamily		
Tumor necrosis factor α	TNFα	TNFR I
Tumor necrosis factor β	TNF β	TNFR II
The Interleukin family (1-18)		
Interleukin-1α	IL-1α	IL-1R I
Interleukin-1β	IL-1β	IL-1R II
Interleukin-1 receptor antagonist	IL-ra	IL-1R I
gp130/Interleukin-6 family		
Ciliary neurotrophic factor	CNTF	gp130/LIFR and CNTFRα
Leukemia inhibitory factor	LIF	gp130/LIFR and LIFR
Oncostatin-M	OSM	gp130/LIFR and OSMα
Cardiotropin-1	CT-1	gp130/LIFR and CT-1R
Interleukin-6	IL-6	gp130 and IL-6R
Interleukin-11	IL-11	gp130 and IL-11R

Major categories of growth factors and cytokines are shown. Note that some ambiguity exists in classification schemes because some proteins can potentially be classified in more than one manner (e.g., p75 can be considered a member of the TNF family as well as a receptor for the Neurotrophins).

Abbreviations: trk, tropomyosin-related kinase; flt, FMS-like tyrosine kinase; flk, fetal liver kinase; c-Ret, a transmembrane receptor tyrosine kinase; GFR, Glial cell line-derived neurotrophic factor receptor; M6P, mannose-6-phosphate receptor; gp130, glycoprotein 130.

Table 2. Changes in Growth Factors and Cytokines after Status

	Type of change	Location of change in hippocampus or EC		Duration of change		Effect on neurogenesis under normal conditions
	Increase or decrease	DGC	other	< 3 day	> 3 day	
Tyrosine kinases						
NGF	Increase	Yes	EC?		X	
BDNF	Increase	Yes	PCL, EC		X	stimulates
NT-3	Decrease	Yes	No		X	
trkB	Increase	Yes	trkBTK- in glia	X	X (glia)	
trkC	Increase?	Yes	No	X		
p75	Increase	No	Only in dying cells			
aFGF	Increase	Yes	PCL, glia	X		
bFGF	Increase	Yes	EC, glia	X	X (CA1)	stimulates
FGFR	Increase	Yes	all lamina	X		
HB-EGF	Increase	Yes		X		
Neuregulin	Increase	?				
ErbB4	Increase	?				
IGFR I	Decrease	No	hilus		X	stimulates
IGFR II	Decrease	No	PCL	?		
VEGF	Increase	No	PCs, glia	X	X(glia)	stimulates
Serine threonine kinases						
TGFβ	Decr. Then Increase	No	glia		X	
GDNF	Increase	Yes	hilus, PCL		X	
c-Ret	Increase	No	glia		X	
GFR	Increase	Yes	hilus		X	
Cytokines						inflammation inhibits
TNFα	Increase	No	glia	X		
IL-1β	Increase	No	glia		X	
IL-1 ra	Increase	No	glia	X		
CNTF	Increase	?	glia		X	
LIF	Increase	Yes	hilus, PCL, glia	X		stimulates
OSM	Increase	?	glia	X		
IL-6	Increase	No	glia	X		inhibits
IL-11	Increase	No	glia, nonprincipal cells	X		

Changes in growth factors after status epilepticus are shown, including which cells demonstrate changes, the duration of changes, and what predicted effects on neurogenesis would be expected based on the available literature in normal hippocampus. EC = entorhinal cortex; PCL = pyramidal cell layer. TrkBTK- = truncated trkB receptors. Nonprincipal cells are those hippocampal neurons besides the granule and pyramidal cells, and some studies use this term to refer to glia as well. Note that different methods to induce status were used, and some of the animals had different durations of status, which could in turn influence growth factor expression, although to date variability in growth factor expression as a function of status duration has not been identified. Remarkably, different studies of status are in considerable agreement. Dark gray reflects increased levels after status; light gray denotes decreases.

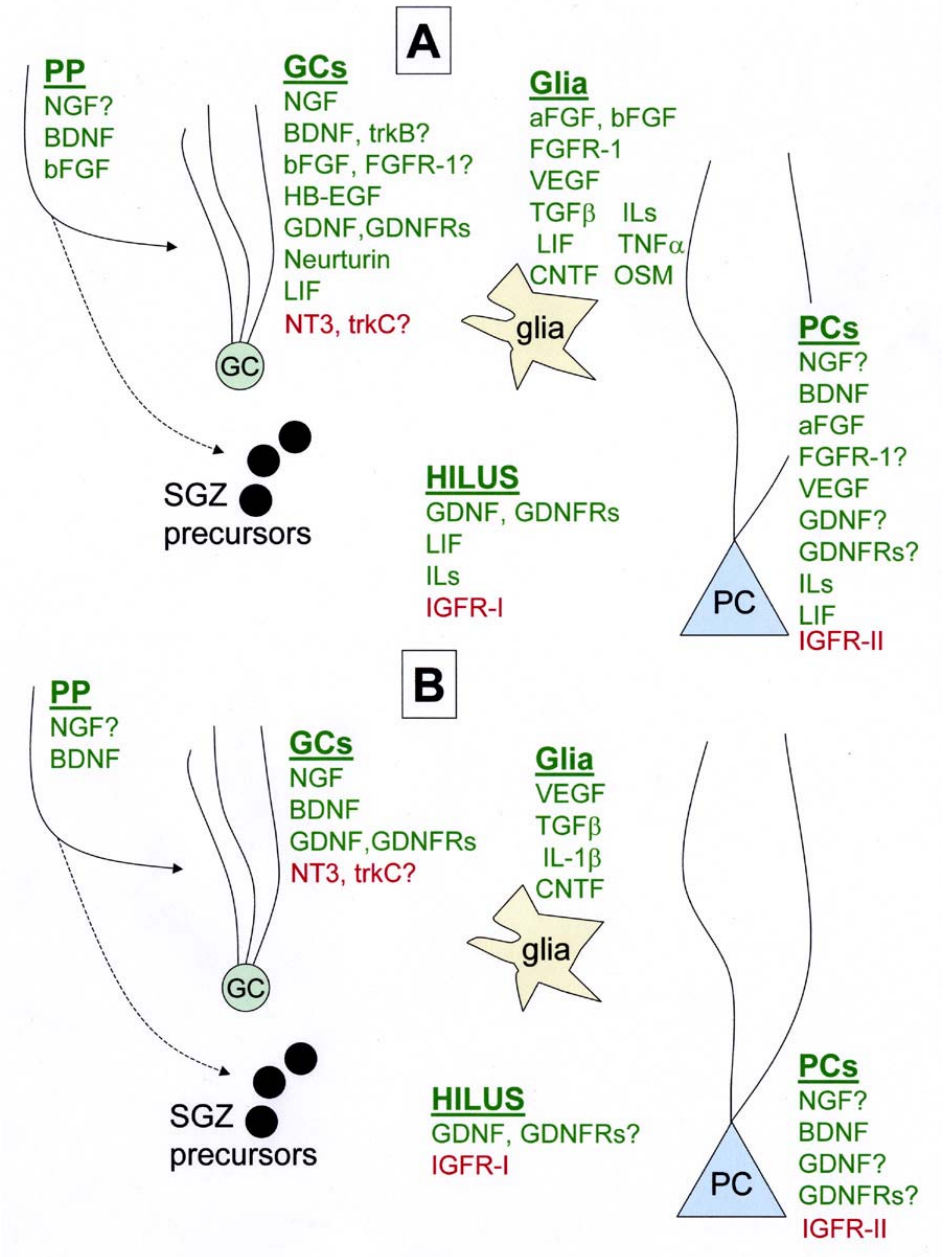

Figure 2. A simplified version of Figure 1 is used to show the changes in growth factors in different cell types after status epilepticus. Data from studies that have induced status by different methods are pooled because they typically have found similar results.

A. Changes are shown that are transient or "acute" (defined here as lasting less than 3 days). Thus, in the PP (Perforant Path), transient elevation (green) in NGF, BDNF and bFGF have been shown. Red indicates decreased expression. Question marks indicate some degree of uncertainty in the literature, either conflicting data, or inability to localize increased expression definitively to the neuron or glia; cell shown in the diagram. For abbreviations, see Table 1. For references, see text.

B. Changes lasting longer than 3 days ("chronic") are shown.

Cell Types Contributing to Growth Factor Effects on Neurogenesis

The discussion above clearly shows that many different types of growth factors increase after seizures, and do so in a location where they are able to exert an effect, potentially, on the SGZ cells. In addition, some may enter the dentate gyrus by the bloodstream, and indeed, it may be no coincidence that the dentate gyrus has some of the densest innervation by capillaries of the brain: the dentate gyrus may "need" the increased vasculature to ensure that neurogenesis can be influenced by factors that aren't expressed in neurons and glia within the dentate gyrus.

Regarding neurons and glia that reside in the dentate gyrus, or innervate that structure, which cells do what to neurogenesis? Seizures induce an initial rise in a number of growth factors over the first hours after seizures within granule cells, cells of origin of the perforant path, hilar neurons, pyramidal cells, and glia. Thus, all of these cells could be effectors. Some of the fastest and most robust changes occur in the granule cells themselves, and perhaps the reason is that they are primarily charged with the responsibility to perpetuate themselves by supplying growth factors to the SGZ. It is interesting to note that some of the other substances made in granule cells could have the same "purpose:" zinc is highly specific to granule cell axons, and clearly causes proliferation of T cells in the periphery; is the same true in the SGZ? The same may be true for the plethora of peptides in hilar neurons, which has puzzled many who have examined the hippocampus to date: perhaps the reason for the presence of these peptides is that they have a concerted and complementary action on neurogenesis. Indeed, neuropeptide Y, which is expressed in dentate interneurons normally, and in granule cells after seizures (Marksteiner et al. 1990; Sperk et al. 1996), is a potent stimulator of neurogenesis (Howell et al. 2003). However, the reason why cells of the dentate gyrus have so many co-localized peptides and such capability to make growth factors is truly unknown.

How would changes in the growth factor concentration of these adult, fully mature cells, spur precursors in the SGZ to divide? One dilemma is a physical one: how to supply the factors, made within the granule cells, for example, to the extracellular compartment of the SGZ. Although the release of growth factors from adult cells can occur in a variety of ways, the major avenues are likely to be 1) diffusion across the plasma membrane, 2) transport through a plasma membrane-bound carrier system, or 3) vesicular release. For granule cells, one has to assume that the increased growth factor concentration is followed by delivery to the processes of the granule cell that lie in the SGZ, the axons, and then one must assume they can be released in some way so that they can reach the progenitors there. Otherwise, growth factor synthesis in the soma must be followed by release there, followed by diffusion to the SGZ without protease attack of the growth factors. The latter seems unlikely given the inability of many of the large growth factors to diffuse readily.

The Influence of Growth Factors on Differentiation, Migration, Synaptogenesis, Survival

Subsequent to the initial hours after seizures, as many of the growth factors that have increased fall back to their normal levels, some remain elevated for days or weeks. These are a much smaller list than those that are elevated initially (Table 2, Figure 2), but perhaps the more interesting group to consider, because they will have the chance to influence the long-lasting changes in neurogenesis, as well as cell differentiation, migration, outgrowth of processes, etc. The list of proteins that remain elevated more than 3 days includes NGF, BDNF, VEGF, TGFβ, GDNF, CNTF, and IL-1β. In addition, NT-3 and IGFR binding remain decreased for long periods after seizures (see above and Table 2).

The long-lasting increases in NGF and BDNF are likely to facilitate many aspects of the differentiation and maturation of newly-born granule cells, given that these neurotrophins mediate such processes in studies of normal granule cells. For example, BDNF has been linked to the survival and neurogenesis of hippocampal neurons (Lowenstein and Arsenault 1996; Katoh-Semba et al. 2002; Lee et al. 2002). Both NGF and BDNF have been shown to stimulate outgrowth of granule cell axons in culture (Holtzman and Lowenstein 1995; Patel and McNamara 1995; Lowenstein and Arsenault 1996). In addition, BDNF appears to have potent effects on the morphology of granule cells *in vivo* (Danzer et al. 2002). Regarding the decline in NT-3, most of the known functions of NT-3 have been identified in dorsal root ganglia and sympathetic neurons, not hippocampus (El Shamy and Enfors 1996; Francis et al. 1999). However, NT-3 has been shown to increase process outgrowth of hippocampal neurons in culture (Morfini et al. 1994), suggesting that a decline in NT-3 would oppose the actions of BDNF and NGF.

The chronic elevation in VEGF is interesting because it could function not only to enable neurogenesis to persist (see above), but also promote angiogenesis that would have additional effects such as increasing blood supply to the newly born neurons. The long-lasting increase in VEGF protein expression appears to be associated with astrocytes, suggesting there could also be other functional roles associated with glia.

The chronic elevation in TGFβ and CNTF may foster increased neurogenesis, because both have been shown to increase the rate of neurogenesis (TGFβ, Hagedorn et al. 2000; CNTF, Jankowsky and Patterson 1999; Emsley and Hagg 2003). TGFβ may also enhance glial survival (Salimi et al. 2003). However, studies of TGFβ *in hippocampus* have not been common. More can be predicted for CNTF, which appears to protect hippocampal neurons (Hagg et al. 1992; Semkova et al. 1999; Naumann et al. 2003). CNTF also has dramatic effects on neurofilaments and neurotransmitter content of hippocampal neurons in culture (Ip et al. 1991).

The protracted elevation in GDNF, which is accompanied by increases in its receptors, could enhance proliferation, given the evidence that GDNF has such an effect on granule cells after ischemia (Dempsey et al. 2003), and GDNF appears to stimulate the cell cycle of photoreceptor progenitors (Insua et al. 2003). GDNF may also help newly-born granule cells survive, given that GDNF is a survival factor for dopaminergic neurons. GDNF and its relative, Neurturin, promote glial survival also (Salimi et al. 2003).

Because pro-inflammatory interleukins are associated with decreased neurogenesis, and IGF with increased neurogenesis (see above), the long-lasting elevation in IL-1β and protracted decline in IGFR binding after seizures would suggest that there are some effects of seizures that oppose the actions described above. It is possible that these negative influences are at least partly responsible for the decline in neurogenesis in the chronic phases of epilepsy that have been observed in human epileptics, and in our studies of pilocarpine-treated rats that were examined 5 months after status (described above).

The Complication: Growth Factors Influence Neuronal Physiology

The discussion above, and in fact most of the work on growth factor effects on neurogenesis, seems to have ignored a large and potentially relevant literature: almost all growth factors identified to date have effects on neuronal physiology. Table 3 lists the effects of growth factors on hippocampal physiological processes, such as synaptic transmission tested *in vitro*, as well as effects on seizures examined *in vivo*. For many that are not on this list, like NGF, there is evidence in other systems that they can influence neuronal activity. Particularly interesting to the current topic are the data showing that growth factors can have potent effects on seizures (Table 3). Therefore, the upregulation of growth factors may not only regulate seizure-induced neurogenesis, but the propensity for seizures as well.

The fact that growth factors not only influence neurogenesis but also influence synaptic transmission, neuronal physiology, and seizures complicates the interpretation of how growth factors influence seizure-induced neurogenesis, because as the growth factors theoretically diffuse to progenitor cells in the SGZ and influence them, they also may act indirectly. Indirect actions could potentially occur by receptors on the precursors, or by changes in the activity of adult neurons in the immediate environment. Furthermore, growth factors could induce receptors and ion channels to develop on progenitors, which in turn would potentially allow them to influence progenitors over a longer time scale. A key issue is that the activity of adult hippocampal neurons influences neurogenesis, neuronal morphology, and many other aspects of hippocampal function (see above).

BDNF is a prime example. There is a substantial body of evidence that BDNF can influence neurogenesis (Linnarsson et al. 2000; Pencea et al. 2001; Katoh-Semba et al. 2002; Lee et al. 2002). However, whether it does so directly, by stimulating the cell cycle for example, is unclear. The difficulty is due to the fact that we know BDNF has potent effects to increase neural activity. It appears to have multiple mechanisms, but all actions increase neuronal activity: BDNF potentiates synaptic transmission (CA1, Kang and Schuman 1995; Korte et al. 1995; Patterson et al. 1996; CA3, Scharfman 1997; dentate gyrus, Messaoudi et al. 1998; for review see Lu 2003), decreases inhibitory transmission (Tanaka et al. 1997; Frerking et al. 1998), and depolarizes neurons by actions on sodium channels (Kafitz et al. 1999; Blum et al. 2002). Therefore, when studies infuse BDNF into the brain and an increase in neurogenesis occurs (e.g., Pencea et al. 2001; Gustaffson et al. 2003; Larsson et al. 2003), one can't be sure that it was due to BDNF directly, or an action of BDNF to increase neuronal activity.

Table. 3. Influence of Growth Factors and Cytokines on Hippocampal Neurons *In Vitro* or Seizures *In Vivo.*

	Acute effects on hippocampal neurons	**Effects on seizures**
NGF		I.c.v. infusion of NGF promotes kindling (1) I.c.v. infusion of antibody to NGF inhibits kindling (19)
BDNF	Potentiates synaptic transmission (7,14,16) Inhibits inhibitory transmission (6,18) Influences sodium channel function (3)	Intrahippocampal BDNF infusion elicits seizures in 33% animals (17) I.c.v. infusion of BDNF scavenger inhibits kindling (2)
NT-3	Potentiates synaptic transmission (7) Promotes paired pulse facilitation (9)	
aFGF		I.p. injections decreases kainic acid-induced seizures (5)
bFGF		Intrahippocampal infusion induces seizures (12) I.c.v. bFGF did not influence kainic acid-induced seizures (11)
TGFβ3		I.c.v. infusion attenuates seizures (8)
GDNF		I.c.v. infusion inhibits kindling development (10) I.c.v. infusion inhibits kainic acid-induced seizures (13)
IL-1β	Mixed effects on LTP (4, 15)	Intrahippocampal infusion exacerbated seizures (20) Infusion of IL-1 receptor antagonist was anticonvulsant (20)
TNFα	Inhibits LTP (4)	

Evidence that growth factors have acute effects on synaptic transmission (effects that occur within hours) or seizures (induction or kindling) are shown. These effects are robust and diverse, and examples provided which show this diversity. These are further discussed in the text. I.c.v. = intracerebroventricular; I.p.= intraperitoneal.

References*:* 1) Adams et al. 1997; 2) Binder et al., 1999; 3) Blum et al., 2002; 4) Butler et al., 2004; 5) Cuevas et al., 1996; 6) Frerking et al., 1998; 7) Kang and Schuman, 1995; 8) Kim et al., 2002; 9) Kokaia et al., 1998; 10) Li et al., 2002; 11) Liu and Holmes, 1993; 12) Liu and Holmes, 1997; 13) Martin et al., 1995; 14) Messauodi et al., 1998; 15) Ross et al., 2003; 16) Scharfman, 1997; 17) Scharfman et al., 2002; 18) Tanaka et al., 1997; 19) Van Der Zee et al., 1995; 20) Vezzani et al., 2002.

Conclusion

Numerous growth factors change after seizures in the cells of the dentate gyrus, in afferents that innervate this region, and in adjacent structures such as the hippocampal formation. We hypothesize that the changes in growth factors caused by seizures play a major role in seizure-induced neurogenesis. In other words, the dentate gyrus has evolved a mechanism to maintain the cell numbers of its primary cell population in the face of stimuli that are damaging to the brain. Although not all the changes that occur in growth factors after seizures can explain the robust increase in neurogenesis, the majority are consistent with this hypothesis. One of the residual puzzles is that most of the changes identified to date are quite rapid, yet the increase in seizure-induced neurogenesis seems to persist for longer periods of time. Whether there has been an underestimation of the persistence in growth factor changes after seizures, or whether other phenomena are involved, will need to be addressed before this puzzle can be solved. But perhaps the greater puzzle is why the dentate granule cells *specifically* need to be so well preserved. In other words, why is it that neurogenesis in the adult brain seems designed to replace only a few cell types, such as granule cells, but not other important cell populations? In the context of seizures and epilepsy, one could argue that the dentate gyrus is in fact of critical importance (Ribak et al. 1992), for example, due to its function as a gate to the hippocampus (Heinemann et al. 1992; Lothman et al. 1992). This function may be much more important than we currently appreciate, and the need to continually maintain granule cell number may be due to the imperative to maintain this barrier. Without it, seizures can much more readily enter hippocampus, cause hippocampal damage, and as many have hypothesized (Bruton 1988; Sutula and Pitkanen 2002), this leads to the sequelae that culminate in chronic epilepsy, and the cognitive deficits associated with it.

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