

Growth factor signaling and memory formation: temporal and spatial integration of a molecular network

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Growth factor (GF) signaling is critically important for developmental plasticity. It also plays a crucial role in adult plasticity, such as that required for memory formation. Although different GFs interact with receptors containing distinct types of kinase domains, they typically signal through converging intracellular cascades (e.g., Ras–MEK–MAPK) to mediate overlapping functional endpoints. Several GFs have been implicated in memory formation, but due to a high level of convergent signaling, the unique contributions of individual GFs as well as the interactions between GF signaling cascades during the induction of memory is not well known. In this review, we highlight the unique roles of specific GFs in dendritic plasticity, and discuss the spatial and temporal profiles of different GFs during memory formation. Collectively, the data suggest that the roles of GF signaling in long-lasting behavioral and structural plasticity may be best viewed as interactive components in a complex molecular network.

Beginning with the pioneering discoveries of Rita Levi-Montalcini, Stanley Cohen, and Victor Hamburger in the 1950s, it is now fully appreciated that growth factors (GFs) are secreted molecules which bind membrane-associated extracellular receptors, thereby activating intracellular signaling cascades that ultimately mediate cellular survival and growth. The first GF that was fully characterized was nerve growth factor (NGF) (Cohen et al. 1954; Levi-Montalcini et al. 1996). Since then, it has become apparent that there are several families of growth factors, and they can be categorized by the signaling mechanism engaged by their receptor. The two major classes of receptors are receptor tyrosine kinases and serine–threonine kinases. GFs that signal through receptor tyrosine kinases include the epidermal growth factor (EGF) family (Prenzel et al. 2001), the fibroblast growth factor (FGF) family (Turner et al. 2006), the platelet-derived growth factor (PDGF)/vascular endothelial growth factor (VEGF) superfamily (Hoch and Soriano 2003; De Almodovar et al. 2009), hepatocyte growth factor (HGF) (Nakamura et al. 2011), and the neurotrophin family, which includes NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5) (Huang and Reichardt 2003; Park and Poo 2013). Those GFs that signal through serine–threonine kinases include the transforming growth factor β (TGF β) superfamily including TGF β , activin, and bone morphogenic proteins (BMPs) (Massague 2000; Krieglstein et al. 2011). There are also families with mixed signaling mechanisms such as the insulin family, including insulin and insulin-like growth factor 1 (IGF1), which signal through receptor tyrosine kinases, and insulin-like growth factor 2 (IGF2), whose primary receptor, IGF2/M6P receptor (also known as the cation-independent mannose 6-phosphate receptor), does not have intrinsic kinase activity (Hawkes and Kar 2004; Taniguchi et al. 2006).

Although there are a wide variety of GFs and distinct receptors that constitute different GF families, there is considerable overlap in the roles that different GFs play as critical mediators of developmental plasticity. For example, GFs are important for promoting cell survival, neurogenesis, differentiation, axon outgrowth, dendritic growth and maturation, synaptogenesis, and activity-dependent synaptic pruning (Hoch and Soriano 2003; Hawkes

and Kar 2004; De Almodovar et al. 2009; Krieglstein et al. 2011; Nakamura et al. 2011; Park and Poo 2013). Surprisingly, different GF families mediate these diverse effects by engaging translation and transcription through highly converging signaling cascades, such as Ras–MEK–MAPK, PI3K–AKT, and CREB-mediated transcription (Finkbeiner et al. 1997; Massague 2000; Prenzel et al. 2001; Huang and Reichardt 2003; Taniguchi et al. 2006; De Almodovar et al. 2009; Acebes and Morales 2012).

In recent years, it has become clear that many of the canonical GF signaling cascades that are engaged during development are re-engaged to support plasticity in the adult. A major form of such plasticity is involved in the induction of learning and memory. Memory can exist in a wide range of temporal domains that can be distinguished not only by the duration of the memory, but also by the molecular mechanisms that are engaged in their induction and maintenance. Short-term memory is mediated by post-translational modifications, and lasts on the order of minutes (Castellucci et al. 1989; Xia et al. 1998). Intermediate-term memory requires protein translation and can last several hours (Sutton et al. 2001; Stough et al. 2006), and long-term memory (LTM) requires both protein translation and de novo gene expression, and lasts for days, months, even a lifetime (Castellucci et al. 1989; Bailey et al. 1996; Sangha et al. 2003; Reissner et al. 2006). In addition to translation and transcription, both LTM and its mechanistic correlate, long-term synaptic strengthening (often termed long-term potentiation [LTP] or long-term facilitation [LTF]), are correlated with dendritic growth and remodeling and synaptogenesis (Lamprecht and LeDoux 2004; Bailey and Kandel 2008; Caroni et al. 2012). Additionally, Ras–MEK–MAPK, PI3K–AKT, and CREB-mediated transcription are all critically important for LTP/LTF and LTM (Bourtchuladze et al. 1994; Yin et al. 1994; Martin et al. 1997; Atkins et al. 1998; Lin et al. 2001; Opazo et al. 2003; Sweatt 2004; Horwood et al. 2006; Lee et al. 2008; Sui et al. 2008; Won and Silva 2008; Alberini 2009). Thus, it is not surprising that a wide range of GFs are implicated as having a critical role in long-lasting plasticity (Abe et al. 1991; Ishiyama et al. 1991; Gutierrez et al. 1997; Zhang et al. 1997; Park et al. 2000; Egan et al. 2003; Sharma et al. 2006; Zhao et al. 2007; Conner et al. 2009; Ageta et al. 2010; McNay et al. 2010; Peng et al. 2010; Chen et al. 2011; Mauerer et al. 2011; Kato et al. 2012; Shioda et al. 2012). There are, however, some conflicting reports for the role of specific GFs in long-lasting plasticity. For example, NGF

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has been demonstrated to be necessary for spatial learning, conditioned taste aversion, and inhibitory avoidance (IA) memory in adult rats (Gutierrez et al. 1997; Conner et al. 2009). However, conditional deletion of *NGF* or *TrkA* in young or intermediate-aged mice did not significantly impair memory for passive avoidance, contextual fear conditioning, or cued fear conditioning (Muller et al. 2012). These data indicate that the role of GFs in specific forms of memory may be more complicated than previously appreciated.

In addition to distinguishing between distinct GF roles in development, compared to their roles in established adult circuitry, rapid progress in this general field raises several important questions. For example, it will be important (1) to determine whether GFs are engaged differentially by different forms of learning and in different brain regions; (2) to establish whether and how GF contributions to long-lasting plasticity change across the lifespan; and (3) to elucidate the relative contributions of individual GFs to learning and memory formation. Because converging signaling cascades are often engaged by different GFs, and phenotypically similar functional outcomes are often induced by different GFs (and even different GF families), the relative contribution of each individual GF is difficult to determine. Are all GFs engaged during learning and memory formation? Does each GF uniquely contribute to a critical aspect of learning and memory? And, if they all mediate similar outcomes through converging signaling cascades, what is the functional significance of more than one GF in the induction of learning and memory?

The central theme of this review is that individual GFs mediate distinct functional outcomes by engaging temporally and spatially regulated signaling cascades. To develop this theme, we will first review data implicating GFs in unique aspects of adult dendritic plasticity. We will then focus on GF regulation of Ras-MEK-MAPK signaling and the distinct spatial and temporal profiles of GFs engaged during plasticity, which could mediate unique functional end points. Finally, we will highlight the fact that a single form of GF signaling does not occur in isolation from other GFs

and their signaling cascades. We thus propose that the wide array of GFs implicated in plasticity is best viewed as interactive elements in a complex molecular network.

Dendritic plasticity

Dendritic plasticity is a fundamental mechanism underlying synaptic strengthening, and is thought to be a critical substrate for the acquisition and consolidation of long-term memories (Bailey and Kandel 1993; Yang et al. 2009). Moreover, dendritic plasticity is not limited to a single brain region; rather, it has been observed in a number of both cortical and subcortical structures (Knafo et al. 2001; Lee et al. 2007; Hofer et al. 2009; Restivo et al. 2009; Xu et al. 2009; Yang et al. 2009; Roberts et al. 2010). Dendrites are highly dynamic and can be modulated by changes in the length of the neck of the spine, by volume changes within the dendrite itself, by dendritic turnover, or by the loss and/or addition of dendrites. All of these forms of dendritic plasticity occur during adult learning and memory (Lamprecht and LeDoux 2004; Segal 2005). Hippocampal-dependent memories are thought to undergo “systems consolidation,” in which storage of the memory over time becomes less dependent on hippocampal structures and more dependent on cortical regions (Frankland and Bontempi 2005). Importantly, dendritic changes in the cortex correlate well with the time frame of systems consolidation (Restivo et al. 2009). Thus, dendritic plasticity provides an excellent candidate mechanism as a platform for studying the acquisition, consolidation, and storage of LTM. Not surprisingly, GFs are critical regulators of adult dendritic plasticity (Horch et al. 1999; Withers et al. 2000; Horch and Katz 2002; Zheng et al. 2003; Dijkhuizen and Ghosh 2005; Ji et al. 2005; Shoji-Kasai et al. 2007; Chiu et al. 2008; Tanaka et al. 2008; Mauceri et al. 2011; Schmeisser et al. 2012; Shioda et al. 2012). Perhaps more surprising is the fact that not all GFs regulate the same aspects of dendritic plasticity (Table 1).

Table 1. GF regulation of dendritic plasticity

	(A) Dendritic and synaptic density	(B) Dendritic length and volume	(C) Dendritic complexity
Tyrosine kinase			
PDGF	Increased dendrites in CA1 of PDGFR-KO mice (Shioda et al. 2012)	No change in length in CA1 of PDGFR-KO mice (Shioda et al. 2012)	No change in CA1 of PDGFR-KO mice (Shioda et al. 2012)
VEGF	No change (no rescue) in spine density in mice with nuclear CaM signaling deficiency (Mauceri et al. 2011)	Increased (rescued) length in mice with nuclear CaM signaling deficiency (Mauceri et al. 2011)	Increased (rescued) in mice with nuclear CaM signaling deficiency (Mauceri et al. 2011)
BDNF	Increased dendrites in cortical and hippocampal culture (Dijkhuizen and Ghosh 2005; Ji et al. 2005)	No change in length in cortical culture (Dijkhuizen and Ghosh 2005)	No change in cortical culture (Dijkhuizen and Ghosh 2005)
	Increased dendrites in cortical slice (Horch et al. 1999)	Increased volume and decreased length in CA1 of hippocampal slice (Ji et al. 2005)	Increased in cortical slice (Horch et al. 1999; Horch and Katz 2002)
Serine-threonine kinase			
TGF β	Increased synaptogenesis in cortical culture (Diniz et al. 2012)		No change in cortical culture (Diniz et al. 2012)
Activin		Increased length in hippocampal culture (Shoji-Kasai et al. 2007)	
BMP		Increased length in hippocampal culture (Withers et al. 2000)	Increased in hippocampal culture (Withers et al. 2000)
Mixed signaling mechanisms			
Insulin	Decreased synaptic density and no change in synapse maturation in <i>Xenopus</i> tectal neurons transfected with DN IR (Chiu et al. 2008)		
IGF2	Increased (rescued) synaptic density and increased (rescued) spine maturation in mouse forebrain with deficient NF- κ B signaling (Schmeisser et al. 2012)		

(KO) Knockout, (IR) insulin receptor, (DN) dominant negative.

Thus, in this review, we use dendritic plasticity as a vehicle to discuss GF signaling for three reasons: (1) it is a well-described component of LTM, (2) it occurs in virtually every brain region implicated in memory formation and storage, and (3) it provides an area that differentiates roles of specific GFs in different components of structural plasticity.

GF regulation of dendritic and synaptic density (outlined in Table 1A)

Mice with mutations in the PDGF β receptor show decreased apical and basal dendrites in the hippocampus, as well as impaired spatial memory (Shioda et al. 2012). However, spine length and dendritic arborization in these mice are similar to control mice (Shioda et al. 2012), indicating that PDGF is important for the number of dendrites, but not for other aspects of dendritic morphology. Similarly, insulin signaling has been shown to support a dissociation in *Xenopus* tectal neurons transfected with a dominant negative insulin receptor (Chiu et al. 2008). These neurons have reduced synapse density and altered activity-dependent dendritic plasticity, but show no difference in synapse maturation (as measured by the area of the presynaptic terminal clustered with vesicles [Chiu et al. 2008]). Another member of the insulin family, IGF2, rescues synapse density and promotes spine maturation in mouse forebrain neurons with a mutation in nuclear factor κ B (NF- κ B) (Schmeisser et al. 2012). Intriguingly, impairments in synaptic signaling due to mutations of NF- κ B signaling are rapidly reversible (within 1 wk of rescue of NF- κ B signaling or within 24 h of IGF2 application), suggesting that this is a highly dynamic regulatory process (Schmeisser et al. 2012).

In cultures of cortical neurons, BDNF increases the number of primary dendrites but not arborization or total dendritic length (Dijkhuizen and Ghosh 2005). Conversely, BDNF increases both dendritic growth and arborization in cortical neuron slice preparation (Horch et al. 1999; Horch and Katz 2002), indicating that BDNF signaling may be different between neurons in culture and those in slice preparations. Finally, in dissociated cultures of mature hippocampal neurons, BDNF increases spine density and the number of primary dendrites, but only the former effect required cAMP (Ji et al. 2005), suggesting that BDNF engages distinct molecular signaling to mediate different structural effects.

GF regulation of dendritic length and volume (outlined in Table 1B)

A TGF β superfamily member, activin, increases the length of dendritic spine necks in a MEK-dependent manner in low-density rat hippocampal cultures (Shoji-Kasai et al. 2007). Another member of the TGF β superfamily, BMP7, increases dendritic length in addition to increasing arborization in hippocampal cultures (Withers et al. 2000). However, unlike these members of the TGF β superfamily, TGF β 1 selectively increases synaptogenesis with no changes in dendritic morphology (Diniz et al. 2012). In addition to its other functions in dendritic density, BDNF mediates spine enlargement and neck shortening at the level of single dendrites in the CA1 region of a hippocampal slice (Tanaka et al. 2008).

GF regulation of dendritic arborization and complexity (outlined in Table 1C)

BDNF release locally elicits a destabilization of dendrites (Horch et al. 1999) and an increase dendritic arborization (Horch and Katz 2002) in cortical slices. Surprisingly, in hippocampal neurons expressing CAMBP4, which blocks nuclear calcium/CaM signaling, VEGFD, but not other members of the VEGF family (VEGF or VEGFC), rescues the reduction in dendrite length and complex-

ity without restoring spine density (Mauceri et al. 2011). Importantly, RNAi depletion of VEGFD in the hippocampus of mice produces a deficit in memory measured in the Morris water maze, but does not affect acquisition of the task. Moreover, impaired contextual fear conditioning, a hippocampus-dependent task, tested at 24 h is also observed in VEGFD-depleted mice (Mauceri et al. 2011).

At this stage of the review it is important to emphasize two caveats. First, most of the studies reviewed here examine GF regulation of dendritic plasticity in culture, which may not engage the same signaling pathways as those in intact adult circuits. Indeed, BDNF seems to mediate different dendritic changes in cortical neuron culture and in cortical slice (Horch et al. 1999; Horch and Katz 2002; Dijkhuizen and Ghosh 2005). Second, dendritic plasticity is certainly not the only cellular platform upon which long-term memory is dependent. Presynaptic signaling is also critically important and, by extension, GF regulation of presynaptic signaling is certainly another major candidate site for plasticity contributing to memory formation. That said, in restricting our review to a consideration of the wide array of effects on dendritic structure and plasticity mediated by a wide range of GFs, an important emergent principle is that no single form of GF signaling can account for all these effects. Thus GFs must be considered as cooperative and integrative elements in explaining the composite effects on dendritic structure that are thought to be a substrate for learning and memory. This view will critically inform any theory of hippocampal and cortical plasticity thought to underlie the consolidation and storage of LTM.

Spatial and temporal regulation of GF signaling

It is striking that distinct regulation of different aspects of adult dendritic plasticity is mediated by different GFs, given that GFs engage convergent signaling mechanisms. To begin to understand how these distinct effects are mediated, one must consider: (1) how the regulation of a single canonical signaling molecule might be differentially regulated by different GFs; (2) when during the induction of memory GF signaling is required; and (3) where within a cell and/or brain region GF signaling is engaged during memory formation.

MAPK activation

The Ras–MEK–MAPK signaling cascade is an evolutionarily conserved pathway that is required for many forms of LTP/LTF and LTM, and is activated by a wide variety of extracellular stimuli, including GF signaling (Adams and Sweatt 2002; Sweatt 2004). Once activated, MAPK can mediate both translation (Kelleher et al. 2004; Tsokas et al. 2007) and transcription (Adams et al. 2000; Davis et al. 2000; Philips et al. 2013). Given the diverse mechanisms upstream of MAPK activation and the diverse outcomes that its activity mediates, MAPK has been postulated to be a critical “node” of plasticity underlying memory formation (Reissner et al. 2006).

MAPK activation is canonically downstream of receptor tyrosine kinase activation triggered by GF binding (Huang and Reichardt 2003; Purcell et al. 2003; Reichardt 2006). TGF β superfamily signaling is mediated primarily either by SMAD-dependent pathways (Massague 1998) or MAPK-dependent pathways (Hartsough and Mulder 1995; Shoji-Kasai et al. 2007), although some crosstalk between these pathways has been reported (Yue and Mulder 2000). Interestingly, IGF2 signaling via the IGF2/M6P receptor, which has no intrinsic kinase activity of its own and is commonly associated with endocytosis and lysosomal targeting (Hille-Rehfeld 1995; Hawkes and Kar 2004), requires MAPK to mediate critical developmental functions (McKinnon et al. 2001).

MAPK signaling is extremely dynamic, and can be regulated both temporally and spatially in a number of different ways (Adams and Sweatt 2002; Reissner et al. 2006; Kholodenko et al. 2010). For instance, MAPK is activated in different temporal phases, both during and after training, which induces long-term synaptic and behavioral plasticity (Atkins et al. 1998; Sharma et al. 2003; Ajay and Bhalla 2004; Philips et al. 2007; Ye et al. 2008, 2012; Pagani et al. 2009; Shobe et al. 2009; Michel et al. 2011a; Philips et al. 2013). Importantly, each temporal phase can be of critical consequence to LTM induction and maintenance (Atkins et al. 1998; Sharma et al. 2003; Michel et al. 2011a; Ye et al. 2012; Philips et al. 2013).

Intriguingly, GFs can independently activate MAPK with different temporal profiles. Many GFs are capable of rapidly activating MAPK. For instance, in *Aplysia* sensory neurons, just 5 min of TGF β 1 stimulation is sufficient to induce MAPK activation and MEK-dependent phosphorylation of synapsin (Chin et al. 2002). Similarly, TGF β 2 induces MAPK activation rapidly in epithelial cell culture (by 5 min), and increasing incubation time increases MAPK activation maximally at 30 min, which then decreases by 60 min, despite continuous incubation (Hartsough and Mulder 1995). Interestingly, a mix of EGF, insulin, and transferrin also causes sustained MAPK activation in epithelial cell culture, but the maximum level of MAPK activation is at 5 min rather than 30 min (Hartsough and Mulder 1995), suggesting that the mechanism of MAPK activation by GFs may be at least quantitatively different.

Indeed, Zheng and Quirion (2004) found that IGF1 induces both transient MAPK activation and sustained AKT activation, while BDNF induces sustained MAPK activation and transient AKT activation in cultured hippocampal neurons. Additionally, HGF and BDNF, both of which act through receptor tyrosine kinases, have an additive effect on MAPK activation and dendritic growth in rat cortical neurons (Fensterwald and Martin 2011). These data indicate that, even within the receptor tyrosine kinase family of GFs, MAPK (and other signaling molecules) may be differentially regulated. Importantly, different temporal phases of MAPK activation can induce different functional outcomes. For instance, in rat pheochromocytoma (PC12) cells, both forskolin, which increases cAMP levels, and EGF activate MAPK transiently, and neither is sufficient to induce differentiation; however, when applied together, MAPK activation is now sustained, and differentiation is induced (Yao et al. 1995), suggesting that signaling cascades which converge upon MAPK can act synergistically in generating integrated functional outcomes.

Intriguingly, Casar et al. (2009) reported that the subcellular localization of the g-protein Ras is critical in determining substrate specificity downstream of MAPK activation. EGF receptor phosphorylation occurs mainly when MAPK activation arises from lipid rafts, whereas phosphorylation of RSK1, a CREB kinase, occurs mainly when MAPK activation arises from the disordered plasma membrane, a distinction which is governed by different scaffolding proteins (Casar et al. 2009). Indeed, the scaffolding molecule kinase suppressor of ras1 (KSR1) is utilized when MAPK is activated by a PKC-dependent pathway, but not a PKA-dependent pathway, and aids the recruitment of specific downstream targets (Shalin et al. 2006). Importantly, KSR1 is required for LTP and associative learning (Shalin et al. 2006). These data raise the possibility that initiation and modulation of GF signaling cascades, as well as GF-induced MAPK activation itself, may have an as yet unappreciated spatial component of regulation.

In summary, GFs can induce unique temporal phases of MAPK activation. A caveat is warranted, however. It is important to note that exogenous GF application used in many of these studies could, in principle, create an abnormal molecular environment, and natural GF signaling in vivo could exert its effects quite differently.

Temporal regulation of GF signaling during plasticity

The engagement of GF signaling cascades has long been known to be very tightly regulated in both space and time throughout development in order to create the precise neural circuits necessary for survival (Heerssen and Segal 2002; Dailey et al. 2005; Ramel and Hill 2012). Thus, it is not surprising that there are temporal windows during which GF signaling is required for the induction of LTP/LTF for LTM. For example, IGF2 mRNA and protein is increased in the dorsal hippocampus 20 h, but not 6 or 9 h, after inhibitory avoidance (IA) training in rats (Chen et al. 2011). Furthermore, IGF2 signaling is required for >1 d, but <4 d, for the consolidation of IA memory (Chen et al. 2011). NGF has also been shown to be required during a restricted temporal window after training. NGF levels in the CA1 region of the hippocampus increased 1 wk, but not earlier or later, after contextual fear conditioning in rats, and antisense knockdown of the NGF receptor TrkA 1 wk, but not 4 wk, after training impaired freezing behavior at test (Woolf et al. 2001). Interestingly, Ageta et al. (2010) found that blockade of activin signaling specifically impaired late phase of LTP (L-LTP) induced by high-frequency stimulation (HFS). In the presence of an activin antibody or follistatin, a natural activin antagonist, HFS L-LTP was, indeed, induced, but decayed to baseline by 9 h. Further, LTP can be enhanced by exogenous activin application or blocked by activin inhibitors 1 h, but not 3 h, after induction (Ageta et al. 2010).

BDNF signaling and regulation is engaged at very early stages in the neuronal response to activity (Tongiorgi 2008). Surprisingly, recent reports indicate that BDNF is also required in additional phases long after training for a memory to persist (Bekinschtein et al. 2007, 2008). Anti-BDNF antibodies or TrkB-Fc chimera, which sequester endogenous BDNF ligand, administered into the dorsal hippocampus of rats prior to training block the formation of LTM for IA tested at both 2 and 7 d (Bekinschtein et al. 2007, 2008; Chen et al. 2012). Interestingly, protein synthesis inhibitors injected into the dorsal hippocampus 12 h after IA training block 7-d, but not 2-d, memory (Bekinschtein et al. 2007, 2008), and this effect can be rescued by co-injection of BDNF (Bekinschtein et al. 2008). A similar deficit is observed using anti-BDNF antibody or BDNF antisense oligonucleotides that are injected 10- to 12-h post-training (Bekinschtein et al. 2007), suggesting that BDNF signaling is initially required at early time points during or after IA training for LTM formation, and a translation-dependent event resulting in the release of BDNF (perhaps even translation of BDNF itself) is required 12 h after training to promote memory persistence out to 7 d. Indeed, BDNF injection into the dorsal hippocampus 12 h after weak IA training—which alone results in a 2-d, but not 7-d, memory—can promote the expression of LTM at 7 d (Bekinschtein et al. 2008). Importantly, this facilitation is temporally limited, as BDNF injection 24 h after weak IA training does not result in memory at 7 d (Bekinschtein et al. 2008).

As evidence accumulates that specific GFs are required in distinct temporal domains for the induction of lasting plasticity and memory, it will be important to determine not only when GF signaling is required for LTM formation, but how modulation of GF signaling both within and outside of these temporal windows ultimately affects LTM. Whether and how GFs can interact with signaling cascades that have already been activated, including interactive effects between more than one GF, will be important questions to address in future studies.

Spatial regulation of GF signaling during plasticity

In addition to temporal regulation of GF signaling, GF signaling is also spatially regulated. Although activity-dependent release of GFs occurs at the synapse, GFs also mediate somatic and nuclear

events. Kanhema et al. (2006) showed that BDNF infusion into the dentate gyrus of anesthetized rats induces LTP and enhanced phosphorylation of eukaryotic initiation factor 4E (eIF4E) and elongation factor-2 (eEF2), which are implicated in enhanced protein synthesis and long-lasting plasticity (Richter and Klann 2009). However, in samples enriched for synapses, BDNF caused a rapid and transient phosphorylation of eIF4E with no effect on eEF2 (Kanhema et al. 2006). These data indicate that BDNF can enhance translation in two different ways (via initiation and via elongation). Initiation is specifically enhanced at the synapse, whereas elongation may be enhanced in the soma or cell-wide. Interestingly, regulation of both synaptic initiation and global elongation was MEK-dependent (Kanhema et al. 2006), suggesting BDNF can engage the same signaling mediator (perhaps in different cellular compartments) for spatially segregated outcomes. Chen et al. (2012) also showed that, after IA training, BDNF is capable of regulating the phosphorylation state of a number of proteins at the synapse important for LTM formation, including CAMKII α , MAPK, and AKT. Importantly, CREB phosphorylation, which is specifically a nuclear protein, was also modulated by BDNF, indicating that BDNF affects both synaptic and somatic targets.

Additionally, in many cases, a GF binding to its receptor can cause endocytosis of the entire GF–GF receptor complex. This is well documented in the case of retrograde signaling endosomes of NGF and BDNF, where the GF–GF receptor complex travels from the synapse to the soma to regulate nuclear events (Zweifel et al. 2005), EGF–EGF receptor endocytosis (Baulida et al. 1996), and IGF2 clearance via the IGF2 receptor (Lau et al. 1994; Hawkes and Kar 2004). Interestingly, protein kinase C (PKC)-mediated phosphorylation of the EGF receptor can cause it to be sorted into a pool for recycling rather than for degradation (Bao et al. 2000). Since PKC is also implicated as a major player in LTM formation (Olds and Alkon 1993; Serrano et al. 1995; Bonini et al. 2005; Michel et al. 2011b), GF–GF receptor endocytosis and subsequent recycling or degradation, could be a potent regulator of EGF signaling and both spatially and temporally specific plasticity.

GFs have also been reported to preferentially modulate certain cell types. NGF is indispensable for the survival of basal forebrain cholinergic neurons (Van der Zee et al. 1995; Chen et al. 1997; Niewiadomska et al. 2011; Allard et al. 2012). NGF deprivation (by repeated injections of anti-NGF antibodies) in the insular cortex disrupts insular cortex–cholinergic basal forebrain connections, causes a substantial decrease in acetylcholine release following high potassium stimulation, and impairs acquisition of conditioned taste aversion and contextual fear conditioning (Gutierrez et al. 1997). Interestingly, expression of a previously conditioned taste aversion memory (pre-NGF deprivation) is not impaired (Gutierrez et al. 1997), suggesting that cholinergic cells mediate acquisition of memories but are not responsible for storage or expression of memory. Similarly, Conner et al. (2009) found that septal NGF was required for hippocampal LTP and LTM. Interestingly, cholinergic cells are highly susceptible to Alzheimer's disease (AD) pathology (Auld et al. 2002; Mesulam 2004), and NGF has been used as a successful therapy in aged rodents and an AD model (Fischer et al. 1987, 1991; Backman et al. 1996; Frick et al. 1997; Capsoni et al. 2012). NGF effects in young adult rodents is conflicting (Van der Zee et al. 1995; Backman et al. 1996; Muller et al. 2012), indicating that the therapeutic effects of NGF may only be exerted in impaired states (Fischer et al. 1991; Janis et al. 1995; Backman et al. 1996) and may actually impair memory in the absence of pathology (Backman et al. 1996).

Interestingly, FGF is known to be a potent modulator of dopamine neurons (Otto and Unsicker 1993; Mena et al. 1995; Takayama et al. 1995; Grothe and Timmer 2007). It increases dopamine metabolism, striatal F-DOPA uptake, the number of

dopamine neurons, and motor function in a nonhuman primate model of Parkinson's disease (Fontan et al. 2002). To our knowledge, the efficacy of FGF to modulate striatal- or dopamine-dependent plasticity is not yet understood, though its role in fear memory and extinction is well described (Graham and Richardson 2011).

More than a century of research examining brain–behavior relationships in the general context of learning and memory has clearly revealed that memory for different learning tasks can be processed in different brain regions. After training, an IGF2 injection is capable of enhancing IA memory if injected into the hippocampus, but not the amygdala (Chen et al. 2011), suggesting that although both the hippocampus and amygdala are important for IA memory, IGF2 is selectively recruited by the hippocampus in this task. BDNF is an important regulator of hippocampal plasticity and hippocampus-dependent memory, but can also modulate amygdala-dependent plasticity (Rattiner et al. 2004, 2005; Meis et al. 2012). Indeed, BDNF signaling is required for LTP induced in thalamus–amygdala connections, but is not required for LTP induced at cortex–amygdala connections (Meis et al. 2012), suggesting that BDNF may have varied, but restricted, roles in different brain regions. Interestingly, in an object recognition task, BDNF release is increased following training and after 24-h testing in both the dentate gyrus and perirhinal cortex (Callaghan and Kelly 2012). In the dentate gyrus, BDNF release is correlated with an increase in MAPK phosphorylation and c-fos induction after training, but not after testing. In the perirhinal cortex, BDNF release is correlated with c-fos induction after training with no discernible modulation of MAPK phosphorylation (Callaghan and Kelly 2012). These data suggest that spatially segregated BDNF signaling may engage different mechanisms over time during the consolidation of a single object recognition memory.

GF signaling: a molecular network

Taking into account the unique functional outcomes and the distinct mechanistic, temporal, and spatial regulation of GF signaling, it is important to consider how different GF signaling cascades cooperate and interact to modulate plasticity. For instance, in COS-7 cells, IGF1 stimulation engages the canonical IGF1 signaling cascade as well as induces the transactivation of EGF receptor, which then activates its canonical signaling cascade (Roudabush et al. 2000), suggesting that some GFs may be able to induce other GF signaling cascades by ligand-independent intracellular mechanisms. Furthermore, GFs can also stimulate the expression of other GFs. IGF1 administration after experimentally induced brain trauma not only stabilizes BDNF and NT3 levels (which decrease in certain areas after trauma), but enhances those levels (Kazanis et al. 2004). Similarly, IGF1 receptor signaling is required for the up-regulation of BDNF mRNA and protein in response to exercise (Ding et al. 2006).

In developing basal forebrain neuron culture, BMP9 increases NGF protein expression and secretion, which in turn increases acetylcholine production (Schnitzler et al. 2010). Similarly, in embryonic cutaneous cells, stimulation with TGF β 1, 2, or 3 induces a biphasic induction of NGF mRNA: (1) an abrupt, early rise that decays after 2 h and (2) a more gradual increase from 12 to 48 h (Buchman et al. 1994). Interestingly, although all TGF β isoforms show this profile, TGF β 1 induces the largest increase in NGF mRNA during the first phase, while TGF β 2 induces the largest increase in NGF mRNA during the second phase (Buchman et al. 1994), suggesting a difference in mechanism or efficiency of TGF β signaling at different time points.

Some GFs actually require other GF signaling cascades for their own functional outcomes. For instance, the neuroprotective effect of basic FGF after acute excitotoxic brain injury induced by

kainic acid in the CA3 region of the hippocampus requires the induction of activin A (Tretter et al. 2000). Additionally, Dennis and Rifkin (1991) reported that migration inhibition by TGF β in wound cultures of bovine aortic endothelial cell culture requires latent TGF β to bind to IGF2/M6P receptor, which induces its conversion to the mature, active form of TGF β . Indeed, a mannose 6-phosphate domain is found in the latent version of TGF β 1 (Purchio et al. 1988), suggesting that IGF2 receptor may be a limiting factor in the conversion and subsequent action of TGF β . Whether IGF2 receptor is required for the functional actions or signaling engagement of TGF β in adult plasticity remains to be elucidated.

Conclusion

It is now widely appreciated that GFs are critical regulators of both developmental and adult plasticity. What remains to be elucidated is how specific GFs exert their effects to form long-lasting behavioral and structural plasticity. We have reviewed data indicating that GF signaling is dynamically regulated in both space and time during learning and memory formation. Furthermore, it is now clear that focusing on a single GF is not sufficient to account for all the structural changes that occur at dendrites during experience-dependent plasticity. Rather, GFs should be considered as elements within an interactive network.

Underscoring the importance of the notion of GF networks is the fact that, because of their secretion and extracellular ligand-receptor binding domains, GFs are potentially powerful therapeutic targets for many neurological diseases and disorders. If individual GFs mediate only a subset of the molecular requirements for the induction of learning and memory, then a therapeutic system based on a single GF may not be sufficient to rescue learning and memory deficits. One must consider (1) the effect of a more global delivery of several GFs or GF agonists in specific therapies, (2) the time at which GF is delivered, and (3) whether the GF will antagonize or enhance other GF signaling pathways. For instance, in the CA1 region of the hippocampus, the number of neurons expressing high levels of BDNF increases by only ~2% 24 h after contextual fear conditioning (Chen et al. 2007). A global increase in BDNF could, in principle, cause more harm than good. Indeed, overexpression of BDNF has been reported to increase anxiety-like behavior, seizure activity, and impair some forms of memory (Croll et al. 1999; Govindarajan et al. 2006; Cunha et al. 2009; Papaleo et al. 2011).

In conclusion, the central theme of this review is that GF signaling in long-lasting behavioral, cellular, and structural plasticity is best viewed as temporally and spatially regulated within a complex molecular network. While there are certainly additional challenges presented by this view, as it adds to the overall complexity of the problem, there are benefits as well. From a basic scientific perspective it can open new avenues for productive inquiry, and from a clinically relevant perspective, it can, in principle, suggest novel approaches to therapies addressing cognitive impairments that accompany a wide range of neurological disorders.

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