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Identifying Molecular Mediators of Environmentally-Enhanced Neurogenesis

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Abstract

Adult hippocampal neurogenesis occurs throughout life and supports healthy brain functions. The production of new neurons decreases with age and deficiencies in adult neurogenesis are associated with neurodevelopmental and degenerative disease. The rate of neurogenesis is dynamically sensitive to one's environmental conditions and experiences, and certain stimuli are known to robustly enhance neurogenesis in rodent models, including voluntary exercise, enriched environment, and electroconvulsive shock. In these models, information about an organism's environment and physiological state are relayed to neurogenic cell types within the hippocampus through a series of tissue and cellular interfaces, ultimately eliciting a neurogenic response from neural stem cells and newborn neurons. Therefore, understanding how novel genes and proteins act in specific cell types within this circuit-level context is of scientific and therapeutic value. Several well-studied neurotrophic factors have been implicated in environmentally-enhanced neurogenesis, and this review will serve to highlight recently-discovered, novel molecular mediators of neurogenesis in response to environmental cues. Furthermore, the contribution of advancing large-scale gene expression and function assessment technology to past, present, and future efforts to elucidate cell type-specific molecular mediators of environmentally-enhanced neurogenesis will be summarized.

Introduction

Neurogenesis, the process by which new neurons are created from stem cells, is the driving force in sculpting the central nervous system during prenatal and juvenile periods of development. In mammals, neurogenesis is known to persist under basal conditions in restricted areas of the brain throughout life; the subventricular zone (SVZ) near the lateral ventricle, and the dentate gyrus (DG) of the hippocampus (Zhao, et al., 2008). The SVZ generates inhibitory neurons that migrate through the rostral migratory stream to the olfactory bulb, while the DG yields excitatory granule cells that integrate into the existing hippocampal circuitry. SVZ neurogenesis has not been confirmed to occur in humans, but hippocampal neurogenesis is thought to play a critical role in supporting normal brain

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Conflict of Interest

The authors declare no competing financial interests.

function throughout life in both human and rodents (Aimone, et al., 2010, Aimone, et al., 2011, Akers, et al., 2014, Clelland, et al., 2009, Deng, et al., 2010, Frankland, et al., 2013, Imayoshi, et al., 2008, Opendak and Gould, 2015). Deficits in adult hippocampal neurogenesis are associated with both neurodevelopmental and degenerative diseases, including autism and Alzheimer's disorders (Balu and Lucki, 2009, Christian, et al., 2014, Donovan, et al., 2006, Kempermann, et al., 2008, Mu and Gage, 2011, Sahay and Hen, 2007, Wegiel, et al., 2010). During adult hippocampal neurogenesis, new neurons are developed from a largely quiescent pool of adult neural stem cells (aNSCs) in a tightly-regulated, multi-step process that includes aNSC activation, lineage determination, proliferation of intermediate progenitors, maturation and survival of newborn neurons, and integration with mature neural networks (Kempermann, et al., 2015).

Neurogenesis can be influenced locally by growth factors and neurotransmitters exchanged by neurons and glia in the neurogenic niche, but also by broader physiological and environmental factors that an animal experiences. The interaction between environment and neurogenesis can be thought of as a series of interfaces through which information is relayed from peripheral sources to the proximal cell types involved directly in neurogenesis within the hippocampus, with the final interface regulating activity of aNSCs and newborn neurons themselves (Figure 1). Certain experiences, such as isolation, aging, and stress, are known to have a negative effect on neurogenesis (Czeh, et al., 2002, Dranovsky and Hen, 2006, Fowler, et al., 2002, Gould and Tanapat, 1999, Gould, et al., 2000, Jin, et al., 2003, Klempin and Kempermann, 2007, Kuhn, et al., 1996, Lieberwirth, et al., 2012, Stranahan, et al., 2006, Warner-Schmidt and Duman, 2006, Xu, et al., 2007), while enriched environment, voluntary exercise, and diet can enhance neurogenesis (Boitard, et al., 2012, Brown, et al., 2003, Clark, et al., 2010, Garrett, et al., 2012, Kobilo, et al., 2011, Lee, et al., 2002a, Lee, et al., 2002b, Lindqvist, et al., 2006, Stangl and Thuret, 2009, Tozuka, et al., 2009, van Praag, 2008, van Praag, et al., 1999, Vivar, et al., 2013, Yu, et al., 2014). There is a rich literature documenting the neurogenic phenotypes that result from these treatments, and there is great interest in understanding what specific molecular pathways and mechanisms are responsible for facilitating the interaction between environment and neurogenesis. Numerous peripheral growth factors and metabolic regulators have been well-studied with respect to their response to physical activity and their roles in adult neurogenesis, and several pathways within the DG have been strongly implicated in environmentally-induced neurogenesis. However, probing molecular changes that occur within aNSCs and newborn neurons themselves has proven to be a major hurdle because these neurogenic cell types are relatively rare and intricately interwoven with more abundant mature neurons and glia in the mixed tissue environment of the DG.

Studying the molecular mechanisms underlying environmentally-enhanced neurogenesis has profound implications for understanding disease mechanisms. Because the progression of most neurodevelopmental and degenerative disorders is the result of both genetic and environmental components, investigating the molecular biology underlying the contribution of environment to adult neurogenesis at proximal levels will help researchers understand the etiology of these diseases and identify effective therapeutic strategies that may act with high specificity in neurogenic cell types. This review will serve to highlight recently discovered molecular mediators of environmentally-enhanced neurogenesis and describe ongoing

efforts and current challenges in identifying novel genes and proteins through advancing large-scale, genome-wide technologies.

Models of environmental influence on neurogenesis

In the context of the environment-neurogenesis interaction, “environment” necessarily refers to both the conditions of an animal’s environment, and how the animal behaves within that environment. For example, the presence of toys and running wheels are conditions of an enriched environment, and an animal experiences those conditions through the actions of exploration and running. Therefore, it becomes impossible to completely dissociate environment from physiology, and these collectively represent an animal’s experiences. Various experimental paradigms have been developed to model aspects of environmental influence on neurogenesis. This review will consider three such models; physical activity (PA), enriched environment (EE), and electroconvulsive shock (ECS).

i. Environmental Enrichment

Environmental enrichment (EE) is defined as housing conditions that provide enhanced sensory, cognitive, or motor stimulation (Zhou, et al., 2017). Such housing conditions may include cardboard rolls, toys, textured ribbons, and running wheels (Monteiro, et al., 2014). EE can also include a component of social enrichment when animals are group housed, or dietary enrichment through the use of non-standard food. In some EE paradigms, conditions are changed every few days to maintain novelty, or exposure to EE is restricted. The contribution of each component of the enriched environment cannot be disentangled *post hoc*, and EE must therefore be considered as a mixture of effects. EE has been shown to promote neurogenesis, angiogenesis, spatial navigation, and pattern separation, as reviewed by Clemenson et al. (Clemenson, 2015).

ii. Physical activity

PA can be considered as a specific, physiological component of EE, and is usually modeled in rats and mice by providing voluntary access to running wheels or by forced running on a treadmill. Recently, it was shown that the presence of a locked wheel alone has an effect on neurogenesis that is distinct from that of running *per se* (Dostes, et al., 2016). Some groups therefore house control animals with a locked wheel to control for the novelty of the object. PA is known to increase proliferation within the DG (Ables, et al., 2010, Olson, et al., 2006, Stranahan, Khalil and Gould, 2006, van Praag, Kempermann and Gage, 1999), as well as dendritic spine density of newborn neurons (Leuner and Gould, 2010, Redila and Christie, 2006, Stranahan, et al., 2007). PA causes a transient increase in DG cell proliferation that returns to basal levels after approximately two weeks, followed by a sustained effect on new neuron production that is attributed primarily to enhanced survival (Kronenberg, et al., 2006). Several cellular mechanisms have been proposed to explain PA-induced proliferation, but none can fully account for all experimental observations at this time (Overall, et al., 2016). In addition to changes in neurogenesis, PA enhances spatial memory in the Morris water maze, Y-maze, T-maze, and radial arm maze tests (Fordyce and Farrar, 1991, van Praag, 2008). For a comprehensive review of the neurogenic, neurophysiological, and

behavioral phenotypes associated with PA, see Vivar et al. (Vivar, Potter and van Praag, 2013).

iii. Electroconvulsive shock

Electroconvulsive therapy (ECT) is a highly effective treatment option for specific forms of depression, mania, and schizophrenia (Aksay, et al., 2016). Compared with PA and EE treatments, ECS is decidedly less natural, and is more analogous to the physiological medical intervention of ECT. In humans, ECT is performed under general anesthesia with muscle relaxants. In early rodent experiments, ECS was performed in awake animals, but modern protocols typically include anesthesia via an inhaled agent (Schloesser, et al., 2015). ECS can be performed as a single, acute shock, or as a chronic course of repeated daily shocks. In 2000, multiple groups discovered that tonic-clonic seizures induced by ECS robustly trigger adult hippocampal neurogenesis (Madsen, et al., 2000, Malberg, et al., 2000, Scott, et al., 2000). More recently, it has been suggested that neurogenesis is required for the antidepressant-like effects of ECS (Schloesser, Orvoen, Jimenez, Hardy, Maynard, Sukumar, Manji, Gardier, David and Martinowich, 2015).

Novel mediators of environmentally-induced neurogenesis

The act of running causes the release of molecules in peripheral tissues that promote structural regeneration of muscle and vasculature, regulate body fluids, and manage glucose and protein metabolism. Many of these compounds are secreted into the blood and cross the blood-brain barrier, where they can modulate pathways involved in hippocampal neurogenesis. Most famous among these proteins are insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), and the hormone adiponectin. These proteins are upregulated in response to PA and can enter the brain to promote proliferation, differentiation, maturation, and survival. These and additional peripheral factors that mediate effects of PA on hippocampal neurogenesis are reviewed by Bolijn and Lucassen (Bolijn, 2015), including leptin, angiotensin II, glucocorticoids, adrenaline, reactive oxygen species, AMP-kinase, peroxisome proliferator-activated receptor (PPAR), PPAR γ co-activator 1α (PGC-1 α), ciliary neurotrophic factor (CNTF), and proinflammatory cytokines.

Quiescent aNSCs residing in the subgranular zone (SGZ) of the DG are maintained through slow, controlled self-renewal. Once activated, aNSCs give rise to proliferating adult neural progenitor cells (aNPCs), which differentiate into nascent granule cell neurons that migrate through the DG, mature, and form synapses with established neuronal networks. Pathways within aNSC/aNPCs and newborn neurons that receive information from exogenous sources represent the final interface between environmental influences and increases in activation, proliferation, differentiation, survival, and maturation. Well-established factors that mediate effects of EE and PA on adult neurogenesis include brain-derived neurotrophic factor (BDNF) (Fang, et al., 2013, Farmer, et al., 2004, Gibbons, et al., 2014, Griffin, et al., 2009, Ji, et al., 2014, Johnson and Mitchell, 2003, Johnson, et al., 2003, Molteni, et al., 2002, Russo-Neustadt, et al., 1999, Tong, et al., 2001) and nerve growth factor (NGF) (Chae and Kim, 2009, Molteni, Ying and Gomez-Pinilla, 2002, Neeper, et al., 1996, Tong, Shen, Perreau, Balazs and Cotman, 2001, Zaben and Gray, 2013). The following section will

highlight recently-discovered, novel mediators of environmentally-induced neurogenesis, which are summarized in Table 1.

i. Adiponectin

Adiponectin is a hormone produced by fat cells that influences numerous physiological processes, including glucose metabolism and inflammation. Although studies dating back to 2002 have investigated adiponectin levels in response to PA due to interest in its role in regulating insulin activity (Ferguson, et al., 2004, Hulver, et al., 2002), it was only recently proven that adiponectin crosses the blood-brain barrier to mediate the pro-neurogenic and anti-depressive effects of PA in mice (Yau, et al., 2014). In this work, Yau and colleagues demonstrated that PA-induced increases in cell proliferation (as measured by BrDU and Ki67) and DCX+ new neuron production was completely ablated in adiponectin knockout animals. The ratio of BrdU/DCX co-labeling was unchanged in the knockout mouse, indicating that adiponectin did not influence the process of neuronal differentiation itself. Because BDNF levels were enhanced by PA in both WT and knockout mice, it is likely that adiponectin acts downstream of BDNF in the response to PA. Finally, application of adiponectin to cultured N2a cells and NPCs concurrently with knockdown of either one of the adiponectin receptors (ADNRs) revealed that adiponectin's interaction with ADNR1, rather than ADNR2, was responsible for adiponectin-elicited cell proliferation. In 2015, Nicolas and colleagues reported that the antidepressant-like effects of EE were mediated by adiponectin through a neurogenesis-independent mechanism (Nicolas, et al., 2015). The same group went on to show that this EE-induced adiponectin pathway reverses the pro-inflammatory phenotype of depressive mice by reducing the inflammatory action of microglia (Chabry, et al., 2015). Therefore, there are likely to be multiple avenues by which adiponectin can influence neurogenesis and brain plasticity in response to both PA and EE.

ii. Cathepsin B

A novel myokine, Cathepsin B (CTSB), was recently shown to be elevated in plasma after exercise, and it was demonstrated that PA-induced neurogenesis and enhanced memory were ablated in CTSB knockout mice (Moon, et al., 2016). The same study suggests that CTSB may exert its effects by positively regulating BDNF within aNPCs; when exogenous CTSB was applied to hippocampal progenitor cells, *Bdnf* transcript levels increased, and inhibition of CTSB conversely reduced *Bdnf*. CTSB has also been implicated in angiogenesis in a meningioma cell line (Tummalapalli, et al., 2007), which could be an indirect mechanism by which CTSB activity may improve nutrient and oxygen delivery to neurogenic cells through enhanced vasculature. In an Alzheimer's disease (AD) model mouse, injections of adeno-associated virus expressing *Ctsb* reduced amyloid-β levels (Embury, et al., 2016). Because exercise is known to counteract cognitive decline in aging and AD (Cotman and Berchtold, 2002, Intlekofer and Cotman, 2013), CTSB may promote brain health through neurogenic and non-neurogenic mechanisms. Considering these recent findings, CTSB represents an interesting potential therapy for brain health, but it remains to be seen whether peripherally administered CTSB can enhance neurogenesis or promote cognitive function.

iii. CX_3Cl1

Microglia are the resident immune cells of the brain, and play important roles in regulating aNSC activity and neurogenesis (De Lucia, et al., 2016, Sierra, et al., 2014, Sierra, et al., 2010). Therefore, genes and proteins in microglia that respond to environmental stimuli may bridge environment and neurogenesis through immune pathways. For example, the chemokine CX_3CL1 (also known as fractalkine or neurotactin) promotes a preponderance of neuroprotective microglia over pro-inflammatory microglia (Cardona, et al., 2006). Vukovic et al. found that wheel running increased hippocampal CX_3CL1 levels, particularly in aged animals (Vukovic, et al., 2012). Furthermore, they demonstrated that co-culturing NPCs from running mice with microglia from sedentary mice abolished the effect of running on enhanced aNPC activity, suggesting that PA-induced CX_3CL1 acts within microglia, which can in turn regulate aNSCs in neurogenesis. The role of CX_3CL1 as an environmentally malleable regulator of the microglia-aNSC interaction was further confirmed when Reshef et al. found that functional deletion of CX_3CL1's receptor, CX_3CR1, which is expressed exclusively in microglia, prevented the effect of EE on neurogenesis (Reshef, et al., 2014). Recently, Littlefield et al. used lipopolysaccharide (LPS) as an immune challenge to reduce neurogenesis in aged mice and found that wheel running prevented the LPS-induced loss of new neurons in a manner that correlated strongly with the proportion of microglia that expressed BDNF (Littlefield, et al., 2015). This indicates that BDNF may have an indirect mechanism of promoting neurogenesis by influencing microglia activity, in addition to its well-studied activity in aNSCs themselves.

iv. Diazepam binding inhibitor

In the adult hippocampus, neurons projecting from the DG to CA3 are recurrently connected with local inhibitory interneurons, and these inhibitory neurons are responsible for determining levels of ambient GABA in the DG. NPCs and their progeny express functional GABA receptors, and GABA signaling is crucially involved in both embryonic and adult hippocampal neurogenesis, influencing progenitor proliferation, fate specification, migration of new neurons, and synaptic integration (Ge, et al., 2007). Pioneering studies by Overstreet-Wadiche and colleagues discovered that adult-born new neurons initially receive GABAergic inputs exclusively (Overstreet Wadiche, et al., 2005), and later revealed the importance of GABA signaling in granule cell maturation and experience-dependent synapse un-silencing (Chancey, et al., 2013, Dieni, et al., 2012). In particular, parvalbumin (PV)-expressing interneurons have been shown to synapse directly on proliferating newborn progeny and couple circuit activity to neurogenesis (Song, et al., 2013). Song et al. describe a diametric model in which PV+ neurons simultaneously promote aNSC quiescence through tonic, ambient GABA and survival/maturation of newborn progeny synaptically (Song, et al., 2014). This occurs because, during the first two weeks after a granule cell is born, intracellular Cl^- concentrations are relatively high, and the opening of $GABA_A$Rs results in a net efflux of Cl^- ions and depolarization of the newborn neuron (Owens and Kriegstein, 2002). In contrast, aNSCs with lower intracellular concentrations of Cl^- are inhibited by $GABA_A$R activity. However, it was unclear how PA-induced GABA signaling could result in an increase in proliferation if such signaling would be expected to maintain aNSC quiescence. This was recently resolved by Dumitru et al. (Dumitru, et al., 2017), who demonstrated that diazepam binding inhibitor (DBI), which binds to the benzodiazepine

binding site of $GABA_AR$s, is expressed in aNSCs and serves to reduce GABA currents in these cells, counteracting the negative effect of increased GABA on aNSC proliferation. Furthermore, knockdown of DBI abolished EE-induced increases in the production of DCX + newborn neurons, the number of dividing Ki67+ cells, and the percentage of proliferating aNSCs.

v. Neuropsin

Suzuki et al. investigated the secretory serine protease neuropsin for a potential role in regulating PV+ interneurons in response to EE and PA (Suzuki, et al., 2014). Neuropsin cleaves its target, neuregulin-1 (NRG-1), allowing NRG-1 to interact with p185 (ErbB4) in PV+ interneurons in a neural activity-dependent manner (Tamura, et al., 2012). In neuropsin-deficient mice, the intensity of PV+ terminals was reduced in DG, indicating that neuropsin controls PV activity and GABA signaling in PV-neurons. EE triggered enhanced PV immunoreactivity and elevated hippocampal neuropsin mRNA and protein, suggesting that neuropsin may link environmental stimuli to GABA signaling in PV+ neurons. However, induction of PV by EE was not abolished by deletion of neuropsin, which shows that EE-induced PV induction occurs, at least in part, through a neuropsin-independent mechanism. Whether neuropsin is required for EE-induced neurogenesis remains to be tested.

vi. Tamalin

Yanpallewar et al. (Yanpallewar, et al., 2012) noted that the scaffold protein tamalin (also known as General Receptor for phosphoinositides 1 Associated Scaffold Protein, encoded by the *Grasp* gene) modulated morphine and cocaine sensitivity by altering adaptive neural plasticity involved with addiction, and asked whether Tamalin might influence plasticity in the context of ECS. To this end, they observed a dramatic increase in *Grasp* mRNA within the DG as measured by *in situ* hybridization, which was strongest at 1–3 hours after ECS and returned to basal levels by 24 hours. Interestingly, the tamalin knockout mouse exhibited no defects in basal proliferation and survival of aNPCs, and tamalin is not required for normal development. However, tamalin was required for ECS-induced proliferation, neurogenesis, mossy fiber sprouting, granule cell dendrite arborization, and LTP. Therefore, tamalin may act specifically to facilitate neural plasticity in response to hippocampal neural activity, but no follow-up studies have pursued this intriguing protein as of yet.

vii. Gadd45b

Upregulation of Growth Arrest and DNA Damage inducible Beta (*Gadd45b*) after ECS was first detected in a microarray experiment of rat DG tissue in 2006 (Ploski, et al., 2006). Three years later, it was identified as an immediate early gene in mature hippocampal neurons that is transiently and robustly upregulated after ECS (Ma, et al., 2009). In that study, *Gadd45b* knockout mice did not have significantly altered neurogenesis, but showed reduced levels of proliferation and dendritic development in response to both ECS and 7 days of wheel running. Because Gadd45b is known to be an epigenetic modifier, the authors measured methylation levels of key neurogenic genes in WT and KO animals. They found that ECS induced demethylation of regulatory elements within *Bdnf and Fgf1* in WT animals, but failed to do so in KO littermates. In this way, it is thought that transient

increases in Gadd45b activity may result in long-lasting changes in DNA methylation and neurodevelopment. More recently, the same group expanded upon their work by showing that Gadd45b is essential for ECS-induced proliferation of both quiescent aNSCs and proliferating progenitors (Jun, et al., 2015).

viii. Glycogen synthase kinase-3 β

In addition to activation and proliferation of aNSCs, altering the maturation and survival of newborn neurons can affect the output of neurogenesis. Wnt3 is produced by astrocytes and induces NeuroD1, a proneuronal transcription factor, through the canonical Wnt/β-catenin signaling pathway (Kuwabara, et al., 2009). Wnt3 was observed to increase in DG astrocytes after PA, which was accompanied by enhanced production of neurons in both young and aged mice (Okamoto, et al., 2011). Inhibition of glycogen synthase kinase-3 (Gsk3)-mediated phosphorylation of β-catenin is considered to be the key event in the Wnt/β-catenin pathway (Wu and Pan, 2010). Using a retroviral strategy, it was recently shown by Llorenz-Martin et al. (Llorens-Martin, et al., 2016) that over-expressing Gsk3β specifically in newborn granule neurons resulted in a cell-autonomous impairment of PA-induced maturation, as measured by the number of dendritic spines, the percentage of mushroom spines, and the head diameter of mushroom spines. In this study, however, Gsk3β over-expression also impaired these neuronal development parameters under basal conditions; therefore, it is possible that the action of Gsk3β opposes neuronal maturation generally, and not specifically in the context of PA. Because of its diverse functions, Gsk3 has long been of interest as a therapeutic target (Pandey and DeGrado, 2016). Although over-expression of Gsk3β can restrict the efficacy of PA-induced neuronal maturation, it has not yet been shown that inhibiting Gsk3β can enhance the same processes.

ix. Dynamin-related protein 1

Maturation of new neurons from aNSCs in adult animals requires that energy and metabolic demands be met sufficiently by the developing cell. Dynamin-related protein 1 (DRP1) facilitates mitochondrial fission, and was recently found to be upregulated in the cortex of aged mice in a treadmill running paradigm (Gusdon, et al., 2017). Steib et al. (Steib, et al., 2014) observed that developing neurons undergo dramatic changes in mitochondrial distribution and shape. This group genetically manipulated *Drp1* in the context of PA and discovered that inhibition of *Drp1* impairs neurogenesis, while over-expression enhances PA-induced acceleration of neuronal maturation. Because DRP1 is a critical regulator of mitochondrial function, the effects seen in these experiments may not be attributable exclusively to DRP1, but may instead reflect the broader contribution of mitochondria to PA-induced neurodevelopment. Furthermore, inhibition of Drp1 also diminished neurogenesis under basal conditions, indicating that mitochondria activity is fundamentally coupled to neurogenesis. This notion is supported by experiments in which inhibition of mitochondria activity through ablation of the mitochondrial transcription factor A (*Tfam*) impaired neurogenesis at the intermediate progenitor cell (IPC) level (Beckervordersandforth, et al., 2017). Furthermore, enhanced mitochondrial function ameliorated aging-associated defects in neuronal maturation and in a mouse model of AD (Richetin, et al., 2017). Therefore, it can be concluded that mitochondria are essential for basal and PA-induced neuronal development, and DRP1 is one protein that can be targeted to impact mitochondrial function.

iv. Grf2

Ras-GRF1 (GRF1) and Ras-GRF2 (GRF2) are members of a family of calcium-activated guanine nucleotide exchange factors that can activate Ras and Rac GTP-ases (Feig, 2011). GRF1 was observed to promote survival of new DG neurons (Darcy, et al., 2014a), and EE-enhanced survival of new neurons was ablated in GRF2 KO mice (Darcy, et al., 2014b). GRF2 knockout also impaired LTP through its downstream effector, Erk MAP kinase. Retroviral shRNA knockdown of GRF2 in newborn neurons showed that it promotes survival in a cell-autonomous manner under basal conditions. However, whether GRF2 expressed in aNSCs is critical for EE-enhanced neurogenesis and how GRF2 may exert such a function remain to be explored.

Genome-wide studies of environmentally-enhanced gene regulation

The genes and proteins described so far have been shown to facilitate the environmental impact on neurogenesis through experimental validation. However, many of them were chosen as candidates due to their close relationship to well-established neurogenic pathways. Genome-wide screening techniques allow researchers to cast a broader net when searching for genes that may be involved in the neurogenic response to environmental stimuli, and can offer a big-picture understanding of gene and protein networks acting in concert to coordinate cellular changes. The following sections will discuss unbiased, large-scale studies of gene expression associated with hippocampal neurogenesis in response to PA, ECS, and EE, which are summarized in Table 2. From the historical context of early experiments, progress of the field will be summarized, and recent advancements will be highlighted.

1. Physical activity

Researchers began using microarray technology to measure gene expression in the rat hippocampus in response to PA in the early 2000's. Tong et al. (Tong, Shen, Perreau, Balazs and Cotman, 2001) applied a t-test analysis to microarray data and detected 88 differentially expressed genes (DEGs), equally split between up- and down-regulation after three weeks of wheel running. They observed increases in *Bdnf*, *Vgf*, and genes related to neuronal signaling, plasticity, extracellular matrix, protein trafficking, biosynthetic processes, and immune response. Molteni et al. (Molteni, Ying and Gomez-Pinilla, 2002) normalized array signal to five housekeeping genes and considered expression ratios ≥ 1.8 or ≤ 0.5 to be significantly different after three days, seven days, or 28 days of running, resulting in 15 up-regulated genes and two down-regulated genes. DEGs included key neurotrophins (*Bdnf*, *Ngfb*, *Fgf2*, *Trkb*), synapse-related genes, neurotransmitters, and signal transduction-related molecules. These pioneering studies provided the first glimpse into the global impact of wheel running on hippocampal gene expression. However, these early experiments yielded relatively few individual gene results overall, representing the small but robust tip of a much larger iceberg.

As microarray platforms advanced and granted more power in discerning expression changes, researchers were able to detect hundreds of DEGs in hippocampal tissue after eight weeks of wheel running (Kohman, et al., 2011). In addition to hallmark neurotrophins, such as *Bdnf*, novel regulatory gene networks emerged from this richer dataset. Gene ontology

(GO) analysis implicated chromatin remodeling as a mechanism by which PA facilitates changes in cellular activity within the hippocampus. Lee et al. (Lee, et al., 2014) compared the transcriptional effects of wheel running on rat hippocampus to that of a resistance wheel running paradigm in which wheels were loaded with 30% of the subject's body weight. They determined that intensity of PA has a significant influence on dynamic gene expression, and specifically that the addition of resistance causes a greater number of genes to be down-regulated relative to sedentary controls. Non-resistance wheel running induced changes in metabolism, endocrine system, and molecular transport, and genes altered specifically by resistance wheel running were related to inflammatory/immune response, protein synthesis, and cellular movement. This finding suggests that mild and intense exercise may exert distinct effects on the adult hippocampus. Inoue et al. (Inoue, et al., 2015) used a treadmill running paradigm and concluded that mild exercise below the lactate threshold is more effective than intense exercise in promoting adult neurogenesis as measured by DG cell proliferation. Mild exercise in these experiments led to a greater number of expression changes measured by microarray, but hallmark factors *Bdnf*, *Igf1*, and *Vegf* were unchanged by either treatment. These discrepancies may be due to the timing of tissue collection, as samples were collected two days after the cessation of running, which could allow for running-induced elevation of neurotrophins to subside. Furthermore, the treadmill running design is a forced exercise model that employs mild electric shocks to motivate running, which could introduce an additional stress component to transcriptional perturbations. DEGs in this study were enriched for lipid metabolism, protein synthesis, and inflammatory/immune response, demonstrating a degree of consistency across experiments in biological processes associated with PA despite methodological differences.

Whole hippocampus was used for all the microarray experiments described thus far. One limitation of this approach is that the hippocampal tissue is composed of numerous cell types that are likely to act in transcriptionally distinct ways in response to PA. It would therefore be expected that cell type-specific gene networks would be lost in the bulk output of a such a system. Additionally, a readout of mixed tissue would be biased towards mature neurons, glia, and secreted factors, and biased against rarer NSCs and newborn neurons. One strategy to tailor a microarray experiment more towards neurogenic cell types is to restrict tissue collection to the DG itself, where neurogenesis occurs. Guerrieri and van Praag (Guerrieri and van Praag, 2015) measured gene expression specifically from DG in response to 3 days, 7 days, and 14 days of wheel running and identified novel candidate genes that had not been previously implicated in the brain's response to PA, including upregulation of *Wdr37*, *Armc8*, *Phactr1*, *Zmpste24*, and *Pfkp*. *Armc8* has been linked to carcinogenesis (Fan, et al., 2014), while *Phactr1* is involved in capillary tube formation in endothelial cells (Allain, et al., 2012). It is therefore possible that these developmental genes may contribute to the cellular division processes of neurogenesis and angiogenesis in response to PA.

2. Electroconvulsive shock

Large-scale gene expression studies of ECS began around the same time as those of PA; the first experiment using a custom chip targeting 645 genes in the rat hippocampus in 2003 identified increases in *Bdnf*, *Wnt2*, *Ngf*, *Fgf2*, *Fgfr1*, *Vegf*, *Npy*, *Sst*, *Egr1/2/3*, and *Fos* (Newton, et al., 2003). The following year, Altar et al. (Altar, et al., 2004) used a genome-

wide chip to discern hippocampal gene changes resulting from both acute and chronic ECS. They observed 26 genes specifically changed by chronic ECS, which may be more relevant to the clinical effects of the sustained course of treatment as used in human patients. The same study included cortical tissue, in which only three genes were changed by ECS. The authors interpreted this finding to indicate that the hippocampus is primarily responsible for mediating the chronic effects of ECS. In 2007, Conti et al. performed a microarray study of ECS generated region-specific transcriptional profiles from hippocampus, prefrontal cortex (PFC), frontal cortex (FC), amygdala, hypothalamus, dorsal raphe (DR), and locus coeruleus (LC) (Conti, et al., 2007); in this dataset, hundreds of DEGs were detected in hippocampus, but even more were observed in PFC, FC, amygdala, and especially LC. The large discrepancy between studies of specific brain regions may be due primarily to differences in ECS protocol; Altar et al. utilized one shock per day for 10 consecutive days and collected tissue four hours later, while Conti et al. applied four shocks per day for two days and collected tissue one hour later. The neurogenic niche was targeted by Ploski et al. (Ploski, Newton and Duman, 2006), who used laser capture microdissection to isolate the granule cell layer of the rat DG after ECS treatment. Their microarray data revealed ECS-induced upregulation of *Gadd45b*, *Slc1a1*, and *Ell2*, for which dynamic expression could not previously be detected in whole hippocampus.

In addition to directly measuring gene expression, various techniques have been used to study other mechanisms of gene regulation in response to ECS. By combining chromatin immunoprecipitation (ChIP) with microarray technology, Tanis et al. (Tanis, et al., 2008) profiled promoters bound by the transcription factor CREB. It was observed that hippocampal CREB occupancy and phosphorylation was rapidly enhanced by ECS in promoters of gene networks involved in angiogenesis, neurogenesis, plasticity, and trophic support, supporting a role for CREB as a high-level coordinator of gene transcription in the neurogenic response to ECS. Guo et al. (Guo, et al., 2011) used methyl-sensitive cut counting (MSCC) to quantify CpG methylation in DG tissue at single-nucleotide resolution after ECS, implicating epigenetics as a general mechanism by which ECS-induced neurogenic gene networks are regulated by external stimuli. MicroRNAs (miRNAs), considered to be another form of epigenetic regulation of transcription, were investigated using a microarray containing probes for 350 miRNAs in hippocampus after ECS (O'Connor, et al., 2013). 10 miRNAs were found to change in mice raised under normal conditions, but the effect was much more pronounced in mice exposed to early life stress, as demonstrated by significant changes in 86 miRNAs. These changes exhibited convergence with miRNAs altered by ketamine, suggesting that ECS may exert its anti-depressive effects through epigenetic control by miRNAs. However, functional validation of identified genes is largely lacking.

3. Environmental enrichment

The first genome-wide experiment to investigate the transcriptional effects of EE was carried out in mouse cortex (Rampon, et al., 2000) and showed that EE influences gene expression related to neuronal structure, plasticity, and neurotransmission, although not directly related to neurogenesis *per se*. Early microarray data from the hippocampus of rats housed in an enriched environment for two weeks implicated kinase/phosphatase networks, synapse-

related molecules, transcription factors, metabolic enzymes, and the immune system among 58 EE-modulated genes in the neurogenic niche (Keyvani, et al., 2004). A mouse study using five months of EE detected 41 altered genes (Lazarov, et al., 2005), indicating that EE has long-lasting effects on gene expression. *Gadd45b* was among these genes, which may therefore act as a convergent epigenetic regulator of neurogenesis in response to both EE and ECS.

Future directions and perspective

While genome-wide studies have been performed in hippocampal tissue and specifically within the neurogenic DG, our knowledge of how molecular pathways act across the series of interfaces that relay information to neurogenic cells from an animal's environment remains primitive. To understand how neurogenesis is orchestrated by an interacting network of diverse CNS cell populations, we must be able to attribute gene expression and protein activity triggered by environmental stimuli to their respective cell types. Modern technologies, including translating ribosome affinity purification (TRAP), RiboTag, and fluorescence-activated cell sorting (FACS), have allowed researchers to isolate and purify specific cell types (Okaty, et al., 2011). Single-cell RNA sequencing is also emerging as a powerful tool to achieve unprecedented specificity in gene expression (Poirion, et al., 2016). Researchers can use these approaches coupled with models of environmentally-induced neurogenesis to deduce the transcriptional activity of individual cells in the DG as they respond to environmental stimuli. A recent publication by Lacar et al. (Lacar, et al., 2016) demonstrates such a design with dentate granule neurons. In this study, mice were exposed to 15 minutes of EE and sacrificed one hour later. Single nuclei were dissociated from DG tissue and immunostained for PROX1 and FOS to identify dentate granule neurons that had been activated by EE, and RNA-seq data were generated from both active (PROX1+FOS+) and inactive (PROX1+FOS-) cells. Over 3,000 DEGs were identified, which highlights the degree to which increasing tissue/cell specificity improves the power of gene expression analysis. Up-regulated DEGs were enriched for downstream targets of FOS as expected, and bore other hallmarks of neuronal activity, including genes related to the MAPK pathway, postsynaptic density, and potassium ion transport. Genes more highly expressed in quiescent neurons represented mitochondria activity and DNA repair. This study serves as a proof of concept that transcriptional effects of environmental stimuli can be observed in cell type-specific expression data. This type of data has recently been generated and analyzed from NSCs (Shin, et al., 2015) and newborn neurons (Gao, et al., 2017). Therefore, an effective strategy for studying environmentally-induced neurogenesis will involve combining models of environmental stimuli with transgenic animals and new technology to capture RNA and protein activity within specific neurogenic cell types as they respond to external influences. For a single cell type, information on epigenetic changes can be collected and layered with expression data to gain mechanistic insight of gene regulation. By assessing the parallel activity of the various cell types interacting within DG tissue to regulate neurogenesis, circuit-like models of activity can be constructed to understand the molecular biology at work at the cellular interfaces that transduce an animal's experience into a neurogenic response. Finally, gain- and loss-of-function analysis of identified genes and pathways will validate the roles of novel regulatory factors. Identifying and characterizing key molecules in

this process will inform efforts to develop targeted therapies with specific effects on brain health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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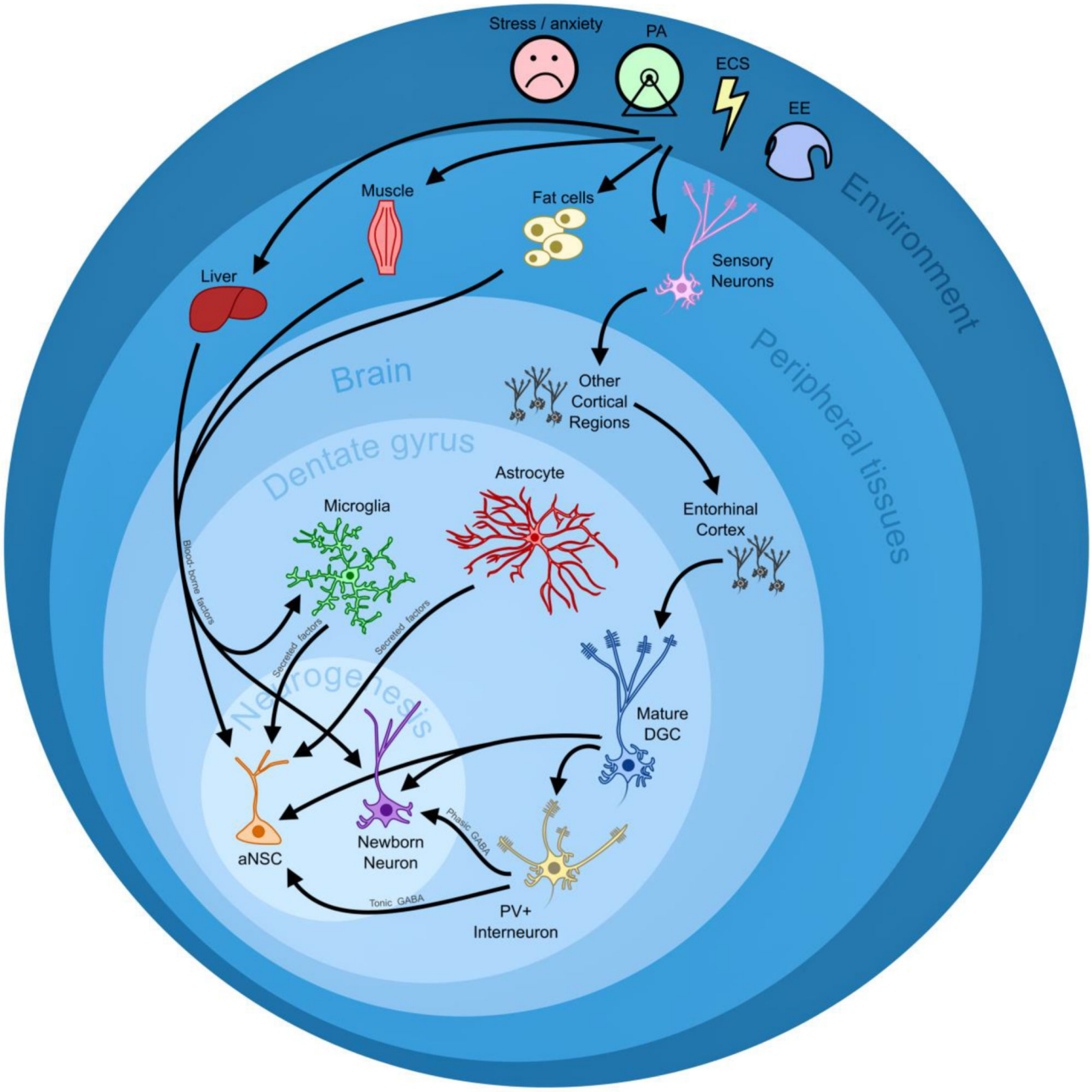

Figure 1.

A schematic of how environmental stimuli and experience can modulate neurogenesis through multiple levels of information relay and interfacing tissue and cell types. Environmental experiences, including stress/anxiety, physical exercise (PA), electroconvulsive shock (ECS), and environmental enrichment (EE) are depicted in the outermost circle. Going inward, concentric circles represent peripheral tissues, brain, dentate gyrus, and the neurogenesis itself. Arrows passing from cell types depicted in outer circles to cell types within inner circles indicate information being relayed across tissue and cell interphases from distal sources to the proximal cell types involved in neurogenesis.

Peripheral tissues communicate with the brain via blood-borne factors and neuronal connections, and cells within the dentate gyrus communicate with aNSCs and newborn neurons via secreted factors and neurotransmitters, such as GABA.

Table 1

Novel mediators of environmentally-induced neurogenesis.

Gene	Protein	Origin	Stimuli/ Experience	Effect on neurogenesis:	Downstream effectors	Reference
Adipoq	Adiponectin	Adipose cell	PA	Promotes cell proliferation and new neuron production, but does not influence differentiation *per se*	ADNR1/AMPK signaling	Yau et al., 2014; Nicolas et al., 2015; Chabry et al., 2015
Ctsb	Cathepsin B	Muscle cell	PA	Enhances number of DCX+ cells	BDNF	Moon et al., 2016
Cx3cl1	C-X3-C Motif Chemokine Ligand 1	Microglia in DG	PA	Enhances NPC neurospheres formed *in vitro*	CX3CR1, BDNF	Vukovic et al., 2012
Cx3cl1 Dbi	C-X3-C Motif Chemokine Ligand 1 Diazepam binding inhibitor	Microgli a in DG aNSCs	PA PA	Enhances NPC neurospheres formed *in vitro* Permits proliferation of GFAP +SOX2+ NSCs	CX3CR1, BDNF Tonic GABA	Reshef et al., 2014 Dumitru et al., 2017
Klk8	Neuropsin; Kallikrein Related Peptidase 8	PV+ interneurons in DG	EE	Modulates PV immunoreactivity in DG; known to regulate LTP and synaptic plasticity; direct role in EE-enhanced neurogenesis not yet shown	NRG-1, ErbB4, GABA signaling	Suzuki et al., 2014
Grasp	Tamalin; General Receptor for phosphoino sitides 1 Associated Scaffold Protein	Neurons or immature neurons in DG	ECS	Permits proliferation of BrdU+ cells; permits LTP formation	Synaptic scaffolding proteins	Yanpallewar et al., 2012
Gadd45b	Growth Arrest and DNA Damage inducible Beta	DG neurons	ECS	Required for ECS-induced (but not basal) proliferation of MCM2+Nestin+ aNSCs and non-radial MCM2+ cells	Demethylates promoter of *Bdnf* and *Fgf1*	Ma et al., 2009
Gadd45b Gsk3b	Growth Arrest and DNA Damage inducible Beta Glycogen Synthase Kinase 3 Beta	DG neurons Immature DG neurons	ECS PA	Required for ECS-induced (but not basal) proliferation of MCM2+Nestin+ aNSCs and non-radial MCM2+ cells Inhibits measures of total and primary apical dendritic length, and number of dendritic branches	Demethylates promoter of *Bdnf and Fgf1* Triggers destruction of β-catenin in Wnt pathway	Jun et al., 2015 Okamoto et al., 2011
Gsk3b Dnm1l	Glycogen Synthase Kinase 3 Beta Dynamin-related protein 1 (DRP1); Dynamin 1 Like	Immature DG neurons Ubiquitously expressed	PA PA	Inhibits measures of total and primary apical dendritic length, and number of dendritic branches Supports survival of labeled newborn neurons	Triggers destruction of β-catenin in Wnt pathway Fundamental in mitochondrial fission	Llorens-Martin et al., 2016 Steib et al., 2014
Rasgrf2	Ras Protein Specific Guanine Nucleotide Releasing Factor 2	Immature and mature DG neurons	EE	Permits enhanced survival of BrdU+ newborn neurons (4 weeks after injection)	Erk MAP kinase	Darcy et al., 2014

This table summarizes information from section 3. Columns include gene symbol, protein, where it is produced, where it exerts its effect, what aspect of neurogenesis it influences, and what downstream molecules it may act through.

Table 2

Genome-wide studies of environmentally-induced gene regulation.

Year	Species	Type of expression analysis	Stimuli/Experience	Duration	Tissue	Reference
2001	Rat	Microarray	Running wheel	3 weeks	Hippocampus	Tong et al., 2001
2002	Rat	Microarray	Resistance running wheel (100 g)	3 days, 1 week, 4 weeks	Hippocampus	Molteni et al., 2002
2008	Mouse	Microarray	Running wheel	16 months	Hippocampus	Stranahan et al., 2008
2011	Rat	Microarray	Running wheel	2 weeks	Hippocampus	Funk et al., 2011
2011	Mouse	Microarray	Running wheel	8 weeks	Hippocampus	Kohman et al., 2011
2013	Mouse	Microarray	Running wheel 3 days per week	6 months	Hippocampus	Alvarez-Lopez et al., 2012
2014	Rat	Microarray	Resistance running wheel (30% body weight)	4 weeks	Hippocampus	Lee et al., 2014
			Running wheel (no resistance			
2015	Rat	Microarray	Forced running on treadmill (mild exercise) 1 hour per day	6 weeks	Hippocampus	Inoue et al., 2015
			Forced running on treadmill (intense exercise) 1 hour per day			
2015	Mouse	Microarray	Running wheel	3 days	Dentate gyrus	Guerrieri et al., 2015
				1 week		
				2 weeks		
2003	Rat	Growth factor chip	ECS: 1 shock		Hippocampus	Newton et al., 2003
2004	Rat	Microarray	ECS: 1 shock per day	10 days	Hippocampus	Altar et al., 2004
2006	Rat	Microarray	ECS: 1 shock per day	10 days	DG granule cell layer	Ploski et al., 2006
2007	Rat	Microarray	ECS: 4 shocks per day	2 days	Prefrontal cortex	Conti et al., 2007
					Frontal cortex	
					Amygdala	
					Hypothalamus	
					Hippocampus	
					Dorsal raphe	
					Locus coeruleus	
2008	Rat	CREB ChIP + microarray	ECS: 1 shock	1 day	Frontal cortex, hippocampus, striatum	Tanis et al., 2008

Year	Species	Type of expression analysis	Stimuli/Experience	Duration	Tissue	Reference
2011	Mouse	Methyl-sensitive cut counting + sequencing	ECS: 1 shock	1 day	DG tissue	Guo et al., 2011
2013	Rat	miRNA microarray	ECS: 1 shock per day	10 days	Hippocampus	O'Connor et al., 2013
2000	Mouse	Microarray	6 hours daily exposure; various toys, wooden blocks, running wheel, and small houses; rearranged every half-day	3–6 hours	Cortex	Rampon et al., 2000
				2–14 days		
2004	Rat	Microarray	24 hours daily; spacious 2-level glass terraria with nesting material, plastic stairs, hemp ropes, pipes, box of soil, wooden blocks, other colored objects; rearranged twice per week	2 weeks	Hippocampus	Keyvani et al., 2004
2005	Mouse	Microarray	3 hours per day for first month, 3 sessions per week for next 4 months; large cages with running wheels, colored tunnels, toys, and chewable material	5 months	Hippocampus	Lazarov et al., 2005
2016	Mouse	Single-nuclei RNA-seq	One 15-minute session; large cages with huts and tunnels	One time	Individual DG neurons	Lacar et al., 2016

This table summarizes published genome-wide studies discussed in section 4.