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Growth Factors and Alcohol Use Disorder

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Neurotrophic growth factors were originally characterized for their support in neuronal differentiation, outgrowth, and survival during development. However, it has been acknowledged that they also play a vital role in the adult brain. Abnormalities in growth factors have been implicated in a variety of neurological and psychiatric disorders, including alcohol use disorder (AUD). This work focuses on the interaction between alcohol and growth factors. We review literature suggesting that several growth factors play a unique role in the regulation of alcohol consumption, and that breakdown in these growth factor systems is linked to the development of AUD. Specifically, we focus on the brain-derived neurotrophic factor (BDNF), glial cell line–derived neurotrophic factor (GDNF), fibroblast growth factor 2 (FGF2), and insulin growth factor 1 (IGF-1). We also review the literature on the potential role of midkine (MDK) and pleiotrophin (PTN) and their receptor, anaplastic lymphoma kinase (ALK), in AUD. We show that alcohol alters the expression of these growth factors or their receptors in brain regions previously implicated in addiction, and that manipulations on these growth factors and their downstream signaling can affect alcohol-drinking behaviors in animal models. We conclude that there is a need for translational and clinical research to assess the therapeutic potential of new pharmacotherapies targeting these systems.

Alcohol use disorder (AUD) is a worldwide problem, characterized by increased alcohol consumption over time, persistent alcohol use despite adverse consequences, and loss of control over alcohol drinking. AUD affects approximately 10%–15% of the population worldwide (World Health Organization 2018; Carvalho et al. 2019) and causes significant health, societal, and economic burdens (McGinnis and Foege 1999; Rehm 2011; Whiteford et al. 2013). Thus, determining the neuroadaptations that control the escalation from moderate-to-compulsive alcohol intake is of great interest to alleviate the societal burden of AUD. Curiously however, although alcohol is widely consumed worldwide, only a minority of the population consume large quantities of alcohol, and an even smaller portion of alcohol users develop a full-blown alcoholism (World Health Organization 2014; Grant et al. 2017). This suggests the existence of innate and/or acquired mechanisms that protect against the transition from

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moderate-to-excessive, uncontrolled, and compulsive alcohol use.

Here, we review studies suggesting that several growth factors are implicated in the endogenous pathways that control the transition from moderate-to-excessive alcohol consumption. Specifically, we focus on brain-derived neurotrophic factor (BDNF), glial cell line–derived neurotrophic factor (GDNF), fibroblast growth factor 2 (FGF2), insulin growth factor 1 (IGF-1), and on anaplastic lymphoma kinase (ALK) and the growth factors that bind to this receptor tyrosine kinase—midkine (MDK) and pleiotrophin (PTN).

Growth factors, originally discovered for their ability to support neuronal development, survival, and differentiation (e.g., Davies et al. 1986; Lin et al. 1993; Ford-Perriss et al. 2001; Muramatsu 2011; Werner and LeRoith 2014), perform a variety of functions in the adult brain, including regulation of neuronal plasticity, learning, and memory (Molteni et al. 2001b; Park and Poo 2013; Zagrebelsky and Korte 2014). Substance use disorders have been characterized as diseases of maladaptive plasticity (Lüscher and Malenka 2011; Feltenstein and See 2013; Nestler 2013) and, thus, alterations in the growth factor systems present putative molecular mediators of the long-lasting effects of drugs of abuse, including alcohol (Alguacil and Herradón 2015; Logrip et al. 2015; Ron and Barak 2016; Barak et al. 2019; Even-Chen and Barak 2019a). In addition, as detailed below, several studies have identified alterations in certain growth factors in the plasma or in the postmortem brains of human AUD patients, further suggesting that growth factors are extremely relevant targets to investigate, and that molecules that can interact with growth factors, their receptors or downstream pathways may provide strong therapeutic candidates.

As detailed below, in most cases, the anatomical focus for the addiction-related action of growth factors is centered in two main brain circuitries, which have been implicated in addiction: the "mesocorticolimbic system," composed of dopaminergic projections from the ventral tegmental area (VTA) to limbic regions (e.g., the nucleus accumbens [NAc], amygdala, hippocampus) and to the prefrontal cortex (PFC) (Koob and Le Moal 2001; Volkow and Morales 2015), and the "nigrostriatal system," composed of dopaminergic projections, form the substantia nigra (SN) to the dorsal striatum (Wise 2009; Everitt and Robbins 2013). Regions comprising these brain circuitries further interact with each other and additional brain regions (Ron and Barak 2016; Abrahao et al. 2017), and, as we discuss below, neuroadaptations in these circuitries may lead to addiction phenotypes.

BDNF

BDNF is a member of the nerve growth factor (NGF) family of neurotrophic factors (Barde et al. 1982; Barde 1994). BDNF signals by binding to tropomyosin-related kinase B (TrkB), a receptor tyrosine kinase that autophosphorylates upon binding to BDNF, initiating downstream signaling via the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phospholipase Cγ (PLCγ), and phosphoinositol 3-kinase (PI3K) pathways (Huang and Reichardt 2003). Both BDNF and TrkB are widely expressed throughout the brain, and particularly in the cortex, hippocampus, and cerebellum (Hofer et al. 1990; Klein et al. 1990). BDNF regulates a variety of neuronal processes, including neuronal development and survival, synaptic plasticity, and learning and memory processes (Castrén 2004; Lu et al. 2008, 2014; Minichiello 2009; Cowansage et al. 2010). In contrast, dysregulation of BDNF function has been implicated in multiple neuropsychiatric disorders (Autry and Monteggia 2012; Castrén 2014), including depression (Koo et al. 2019), schizophrenia (Buckley et al. 2007), and anxiety disorders (Andero et al. 2014), as well as drug abuse (Ghitza et al. 2010; Logrip et al. 2015; Koskela et al. 2017).

BDNF in the mesolimbic dopamine system promotes drug sensitization and self-administration, particularly for cocaine (Horger et al. 1999; Lu et al. 2004; Graham et al. 2007, 2009) but also for opiates (Vargas-Perez et al. 2009; Wan et al. 2011). In contrast, elevating BDNF levels in the medial prefrontal cortex (mPFC) can reverse molecular adaptations

underlying stimulant drug-seeking (Berglind et al. 2007, 2009; Hearing et al. 2008; Sadri-Vakili et al. 2010; Whitfield et al. 2011; Sun et al. 2013).

Alcohol Regulation of BDNF Expression in the Brain

Bdnf messenger RNA (mRNA) expression is elevated in the dorsal striatum in response to acute alcohol exposure, or moderate alcohol consumption (Logrip et al. 2015). Acute injection of alcohol (2 g/kg) significantly increased *Bdnf* mRNA levels in the dorsal striatum of mice (McGough et al. 2004). Importantly, the increase in *Bdnf* mRNA in the dorsal striatum was observed in mice after 4 weeks of voluntary 10% alcohol consumption in an unlimited 2-bottle choice (2-BC) access paradigm that generates moderate levels (~10 g/kg/24 h) of alcohol intake (McGough et al. 2004). BDNF was also elevated after a single 4-h session of 2-BC access (5.6 g/kg intake) under a modified drinking in the dark (DID) paradigm (Logrip et al. 2009). A similar increase in *Bdnf* mRNA expression was observed in the dorsal striatum following rat operant alcohol self-administration of 10% alcohol, with substantially greater alcohol-induced *Bdnf* levels in the dorsolateral striatum (DLS), as compared to the dorsomedial striatum (DMS) (Jeanblanc et al. 2009). Interestingly, these increases in *Bdnf* expression were restricted to the dorsal striatum, with no similar effects in the NAc (McGough et al. 2004; Logrip et al. 2009). Moreover, sucrose consumption did not affect *Bdnf* expression in these brain regions (Logrip et al. 2009). Together these data demonstrate that acute alcohol exposure and chronic alcohol consumption at moderate levels (Dole and Gentry 1984) lead to increased striatal *Bdnf*, which results in BDNF release and activation of TrkB-mediated ERK1/2 signaling (Logrip et al. 2008).

In contrast to the increases in dorsal striatal *Bdnf* mRNA observed following moderate alcohol intake, escalated alcohol drinking following 6 weeks of daily drinking (Rhodes et al. 2007), generated no alteration in *Bdnf* mRNA expression (Logrip et al. 2009). Moreover, long-term consumption of alcohol in the intermittent access to alcohol 2-BC (IA2BC) procedure in which rodents have concurrent access to one bottle containing 20% alcohol and a second bottle containing water, led to increased membranal localization of the low-affinity BDNF receptor, p75 neurotrophin receptor (p75NTR) (Darcq et al. 2016), whose activities oppose those of the TrkB receptor (Kraemer et al. 2014). In addition, long-term excessive alcohol use led to a reduction in the mRNA expression of the growth factor in cortical regions (Logrip et al. 2009), including the mPFC of mice (Darcq et al. 2015) and rats (Tapocik et al. 2014). Relatedly, BDNF protein expression in the mPFC of alcohol-dependent mice was lower compared to nondependent mice (Haun et al. 2018). Taken together, as alcohol consumption can elevate *Bdnf* mRNA expression after 4 or more weeks of moderate drinking, the breakdown of alcohol's ability to up-regulate *Bdnf* expression following higher levels of alcohol intake suggests the possible loss of a protective mechanism.

Interestingly, analysis of the effects of chronic alcohol consumption on different exons of the *Bdnf* gene in the hippocampus showed that alcohol up-regulated the expression of exons II, III, VI IX, but down-regulated the expression of exon VIII, with no effects on exon I and IV expression (Stragier et al. 2015). These expression changes correlate with enrichment in acetylated H3 at *Bdnf* promoter PVI and trimethylated H3 at PII and PIII (Stragier et al. 2015).

Alcohol exposure in protocols of nonvoluntary alcohol exposure were also shown to affect BDNF expression. For example, a short withdrawal from vapor chambers resulted in increased *Bdnf* expression in the hippocampus and hypothalamamic supraoptic nucleus (Tapia-Arancibia et al. 2001). Likewise, the BDNF protein level was increased in the parietal cortex and septal nucleus in rats exposed to alcohol via a liquid diet (Miller 2004; Miller and Mooney 2004), and in the hippocampus, cingulate and motor cortex of rats were withdrawn from an alcohol liquid diet (Alele and Devaud 2013), which leads to very high, nonphysiological levels of alcohol intake. In contrast, *Bdnf*

mRNA was reduced in response to withdrawal from voluntary alcohol drinking in the 2-BC paradigm (Briones and Woods 2013). Finally, an acute injection of alcohol increased BDNF protein levels in the medial (MeA) and central nuclei of the amygdala (CeA) (Pandey et al. 2008), whereas withdrawal in alcohol-dependent rats via liquid diet chronic alcohol exposure led to reduced amygdalar BDNF expression (You et al. 2014).

A possible mechanism for regulating mRNA expression involves microRNAs (miRs), short noncoding RNA sequences that inhibit the translation of mRNA by binding to cytoplasmic mRNA and targeting them for degradation (Bartel 2004). It has been shown that the down-regulation of *Bdnf* expression in the mPFC is associated with elevated levels of two miRs that specifically target *Bdnf* mRNA. Specifically, excessive alcohol consumption increased the expression of miR30a-5p in mice (Darcq et al. 2015), and protracted alcohol withdrawal in dependent rats resulted in increased expression of miR-206 (Tapocik et al. 2014). Importantly, the expression of these miRs negatively correlated with BDNF expression in both paradigms (Tapocik et al. 2014; Darcq et al. 2015). It is also possible that alcohol regulates BDNF in the striatum via altering the expression of other BDNF targeting miRs such as miR124a (Bahi and Dreyer 2013).

Innately lower BDNF expression may provide a predisposition factor in rats for higher alcohol consumption, as alcohol-preferring (P) rats, genetically selected for high alcohol intake and preference (Li et al. 1987), display reduced BDNF protein levels in the NAc (Yan et al. 2005) and the CeA and MeA and bed nucleus of the stria terminalis (BNST) (Prakash et al. 2008; Moonat et al. 2011) relative to the low-drinking nonpreferring (NP) rats. In summary, the surveyed data indicate that while acute or moderate alcohol exposure increases *Bdnf* expression in several brain regions, including the dorsal striatum, and particularly in the DLS, chronic alcohol reduces the expression of the growth factor in the cortex and hippocampus, and lower BDNF expression levels are associated with elevated alcohol consumption (see Table 1 for a summary of the effects of alcohol on brain BDNF expression.)

As BDNF's blood concentration was suggested to reflect the content of the growth factor in the brain (Karege et al. 2002; Klein et al. 2011), studies in humans have attempted to link the peripheral levels on BDNF with factors related to alcohol-drinking behaviors. For example, patients in the state of alcohol intoxication had increased plasma levels of BDNF (Chul et al. 2009; Heberlein et al. 2010). However, studies that examined BDNF levels in alcohol-dependent patients at the time of hospitalization yielded mixed results. While Zanardini et al. (2011) described lower BDNF serum levels in alcohol-dependent patients compared with healthy controls, other studies found no differences between the alcoholic patients and the control subjects (Huang et al. 2008; Heberlein et al. 2010; Costa et al. 2011). Monitoring the peripheral BDNF levels of patients diagnosed with AUD after 10 months of abstinence revealed lower plasma concentrations of BDNF, as compared with control group (García-Marchena et al. 2017). Similarly, a decreased plasma BDNF concentration was reported after a month of withdrawal (Joe et al. 2007). In contrast, elevated levels of serum BDNF were described in alcohol patients after shorter durations of abstinence (Huang et al. 2008; Chul et al. 2009). Further, BDNF serum levels were associated with withdrawal severity during early alcohol withdrawal, but while negative association was reported in one study (Heberlein et al. 2010), positive association was observed in another (Huang et al. 2008). This discrepancy was suggested to result from heritable and environmental variables (Joe et al. 2007; Nubukpo et al. 2017; Sharma et al. 2017). Finally, Heberlein et al. (2015) reported on increased methylation rates of the BDNF promotor of alcoholic patients during early withdrawal, compared with healthy controls, and decrease in methylation during the withdrawal period. Taken together, these findings showing alterations in peripheral BDNF levels during the abstinence period may expand the findings from animal models, suggesting a potential role of BDNF in the maintenance of abstinence.

Table 1. Effects of alcohol on BDNF expression

Treatment regimen	BDNF expression	Effect	References
Acute administration (2 mg/kg), 45 min after injection	mRNA:		McGough et al. 2004
	Hippocampus	↑	
	Dorsal striatum	↑	
	PFC	-	
Voluntary consumption (10% 2-BC), 4 wk	mRNA:		McGough et al. 2004
	Hippocampus	-	
	Dorsal striatum	↑	
	PFC	-	
Voluntary consumption (10% alcohol in operant self-administration), 5 wk	mRNA:		Jeanblanc et al. 2009
	DLS	↑	
	DMS	↑	
Chronic exposure to alcohol vapor, 4 wk	mRNA:		Tapia-Arancibia et al. 2001
After alcohol exposure	Hippocampus CA1	↓	
	Hippocampus dentate gyrus	↓	
	Hippocampus CA2	-	
	Hippocampus CA3	-	
	Hypothalamic supraoptic nucleus	↓	
After 12 h of withdrawal	Hippocampus CA1	↓	
	Hippocampus dentate gyrus	-	
	Hippocampus CA2	-	
	Hippocampus CA3	↑	
	Hypothalamic supraoptic nucleus	↑	
Chronic intermittent ethanol (CIE) exposure	Protein:		Haun et al. 2018
	mPFC, dependent mice vs. nondependent	↓	
Withdrawal from alcohol liquid diet	Protein:		Alele and Devaud 2013
	Hippocampus	↑	
	Cingulate cortex	↑	
	Motor cortex	↑	
Alcohol liquid diet	Protein:		Miller 2004; Miller and Mooney 2004
	Hippocampus	↓	
	Parietal cortex	↑	
	Septum	↑	
Withdrawal from alcohol consumption (2-BC), after 8 d of withdrawal	BDNF:		Briones and Woods 2013
	Hippocampus	↓	
Voluntary consumption (10% 2-BC), 3 wk	mRNA:		Stragier et al. 2015
	Hippocampus		
	exons II, III, VI IX	↑	
	exon VIII	↓	
	exons I, IV	-	
Voluntary consumption (10% 2-BC), 3 wk	Protein:		Stragier et al. 2015
	Hippocampus	↑	
Voluntary consumption (single session of 10% alcohol in limited 4-h access 2-BC)	mRNA:		Logrip et al. 2009
	Dorsal striatum	↑	
	NAc	-	
Voluntary consumption (10% alcohol in limited 4-h access 2-BC), 6 wk	mRNA:		Logrip et al. 2009
	Dorsal striatum	-	
	NAc	-	
	Dorsal PFC	-	
	Ventral PFC	↓	
	Frontal cortex	↓	
	Posterior cortex	↓	

Continued

Table 1. *Continued*

Treatment regimen	BDNF expression	Effect	References
Voluntary consumption (10% alcohol in limited 4-h access 2-BC), after 2 wk of deprivation	mRNA:		Logrip et al. 2009
	Dorsal PFC	-	
	Ventral PFC	-	
	Frontal cortex	↑	
	Posterior cortex	-	
Voluntary consumption (10% alcohol in limited 4-h access 2-BC), after a postdeprivation session of alcohol access	mRNA:		Logrip et al. 2009
	Dorsal PFC	-	
	Ventral PFC	-	
	Frontal cortex	↓	
	Posterior cortex	↓	
Voluntary consumption (5% alcohol 2-BC), 15 d	mRNA:		Bahi and Dreyer 2013
	DLS	↓	
	DMS	-	
Voluntary consumption (IA2BC), 7 wk	mRNA:		Darcq et al. 2015
	mPFC	↓	
Voluntary consumption (10% 2-BC), 21 d	mRNA:		Darcq et al. 2015
	mPFC	-	
Voluntary consumption (IA2BC), 7 wk	TrkB:		Darcq et al. 2016
	DLS	-	
	DMS	-	
	p75NTR in total homogenate:		
	DLS	-	
	DMS	-	
	p75NTR synaptosomal fraction levels of:		
	DLS		
	Binge	↓	
	Session end/withdrawal	↑	
	DMS	-	
Acute administration (1.5 g/kg)	TrkB:		Darcq et al. 2016
	DLS	-	
	p75NTR:		
	DLS	-	
Voluntary consumption (10% 2-BC), 21 d	TrkB:		Darcq et al. 2016
	DLS	-	
	p75NTR:		
	DLS	-	
Alcohol-preferring (P) rats	Protein:		Prakash et al. 2008; Moonat et al. 2011
	Amygdala	↓	
Acute administration	Protein:		Pandey et al. 2008
	Amygdala	↑	
Withdrawal from alcohol dependence (liquid diet)	Protein:		You et al. 2014
	Amygdala	↓	
CIE vapor exposure (4 weekly cycles), 4 wk	*Bdnf* mRNA:		Solomon et al. 2019
	Dorsomedial PFC		
	3-d post-CIE	↓	
	7-d post-CIE	↓	
	Central amygdala		
	3-d post-CIE	↓	
	7-d post-CIE	↓	

Continued

Table 1. *Continued*

Treatment regimen	BDNF expression	Effect	References
	Hippocampus		
	3-d post-CIE	↓	
	7-d post-CIE	-	

(↑) increase, (↓) decrease.

(BDNF) Brain-derived neurotrophic factor, (mRNA) messenger RNA, (PFC) prefrontal cortex, (mPFC) medial PFC, (DLS) dorsolateral striatum, (DMS) dorsomedial striatum, (2-BC) 2-bottle choice, (NAc) nucleus accumbens, (IA2BC) intermittent access to 20% alcohol 2-bottle choice.

BDNF and the Regulation of Alcohol Consumption

Manipulations increasing or decreasing BDNF expression have been shown in animal models to modulate alcohol consumption and have suggested a role for BDNF in the suppression of alcohol intake (see Table 2 for a summary).

Numerous lines of investigation have raised the possibility that BDNF keeps alcohol intake in moderation. Specifically, mice expressing approximately half the normal level of BDNF in the brain showed elevated alcohol intake both under baseline conditions (Hensler et al. 2003) and after a period of abstinence (McGough et al. 2004). Heterozygote of BDNF knockout mice also exhibit higher alcohol-induced sensitization and increased preference for an alcohol-paired location, relative to wild-type (WT) mice (McGough et al. 2004). Similarly, mice heterozygous for the transcription factor CREB have a reduced level of BDNF and higher alcohol preference, compared to WT mice (Pandey et al. 2004). Furthermore, conditional deletion of BDNF in mice postnatally (Rios et al. 2001) resulted in elevated alcohol intake (Logrip et al. 2015).

Furthermore, systemic or intradorsal striatum administration of RACK1, a protein that increases BDNF levels (Yaka et al. 2003; McGough et al. 2004; He et al. 2010; Neasta et al. 2012), reduced alcohol intake in mice and rats (McGough et al. 2004; Jeanblanc et al. 2006). Conversely, both BDNF haploinsufficiency (McGough et al. 2004) and the Trk inhibitor K252a (Jeanblanc et al. 2006) prevented the effect of Tat-RACK1 on alcohol drinking. Thus, these data demonstrate an inverse association between BDNF expression and alcohol consumption, likely conveyed via BDNF's action in the dorsal striatum.

Further studies have demonstrated that BDNF's actions to suppress alcohol intake are localized to the DLS. Specifically, infusion of recombinant BDNF into the DLS of rats decreased alcohol self-administration (Jeanblanc et al. 2009). In contrast, down-regulation of the endogenous BDNF in this brain region via viral-mediated delivery of RNAi targeting the *Bdnf* gene increased rat alcohol self-administration (Jeanblanc et al. 2009). In line with these findings, short hairpin RNA (shRNA)-mediated knockdown of *Bdnf* in the DLS, but not in the DMS, also promoted the development of excessive alcohol drinking in rats (Jeanblanc et al. 2009; Logrip et al. 2015). Moreover, infusion of BDNF into the adjacent NAc did not affect alcohol intake. Furthermore, the effect of BDNF in the DLS is specific for alcohol and does not generalize to other consummatory behaviors, as sucrose consumption is unaltered upon the manipulation of BDNF signaling in the DLS of rats (Jeanblanc et al. 2009; Darcq et al. 2015). Together, these data support a role for endogenous BDNF in the DLS in maintaining moderate levels of alcohol intake.

Interestingly, the suppression of alcohol self-administration by intra-DLS administration of BDNF occurred after 3 h (Jeanblanc et al. 2009), a time point indicative of a mechanism requiring downstream signaling and transcription/translation. Indeed, inhibition of protein synthesis prevented the suppression of alcohol self-administration by intra-DLS BDNF infu-

Table 2. Effects of BDNF-related manipulations on alcohol-related behaviors

BDNF manipulation	Behavioral procedure	Effect	References
Bdnf$^{+/-}$ mice	Alcohol consumption and preference (2-BC)	↑	Hensler et al. 2003
Bdnf$^{+/-}$ mice	CPP	↑	McGough et al. 2004
	Alcohol consumption after withdrawal (2-BC)	↑	
Bdnf$^{+/-}$ mice	10% alcohol operant self-administration	-	Hogarth et al. 2013
	Active-lever presses during acquisition sessions	-	
	Breakpoint during progressive-ratio sessions	-	
	Active lever presses during extinction sessions	-	
	Active lever presses during cue and alcohol-induced reinstatement sessions	↑ (females only)	
Inhibition of the BDNF signaling pathway using Trk receptor inhibitor K252a	Alcohol consumption (10% 2-BC):		Jeanblanc et al. 2006
	Bdnf$^{+/+}$ mice	↑	
	Bdnf$^{+/-}$ mice	-	
Increased BDNF expression via Tat-RACK1	Alcohol consumption and preference (2-BC)	↓	McGough et al. 2004
Increased BDNF expression via Tat-RACK1	Alcohol-induced locomotor activity	↓	McGough et al. 2004
Increased BDNF expression via Tat-RACK1 into the dorsal striatum	Alcohol consumption (10% alcohol in operant self-administration)	↓	Jeanblanc et al. 2006
Increased BDNF expression via Tat-RACK1 (1 μm, weekly i.c.v. injection)	Alcohol consumption (10% 2-BC)	↓	McGough et al. 2004
Viral-mediated *Bdnf* knockdown	Alcohol consumption (10% alcohol in operant self-administration):		Jeanblanc et al. 2009
	Infusion into the DLS	↑	
	Infusion into the DMS	-	
BDNF infusion	Alcohol consumption (10% alcohol in operant self-administration, 3 h after infusion):		Jeanblanc et al. 2009, 2013
	Infusion into the DLS	↓	
	Infusion into the DMS	↓	
	Infusion into the NAc shell	-	
Infusion of BDNF antisense ONDs/ BDNF sense ONDs/BDNF + BDNF antisense ODNs/BDNF	Alcohol preference (7% 2-BC)		Pandey et al. 2006
	Infusion into the central amygdala:		
	Bdnf antisense ODNs	↑ (antagonized by coinfusion of BDNF)	
	Infusion into the medial amygdala:		
	Bdnf antisense ODNs	↑ (antagonized by coinfusion of BDNF)	
	BDNF	↓	
	Infusion into the basolateral amygdala	-	

Continued

Table 2. *Continued*

BDNF manipulation	Behavioral procedure	Effect	References
Bilateral infusion of BDNF (0.50 μg) into mPFC of dependent or nondependent mice	Alcohol intake (15% 2-BC) Dependent mice injected with BDNF vs. dependent mice injected with vehicle	 ↓	Haun et al. 2018
Viral-mediated overexpression of *Bdnf* in the mPFC	Dependence-driven escalation of alcohol drinking (15% 2-BC)	↓	Haun et al. 2018
Viral-mediated BDNF overexpression or down-regulation of miR124a in the DLS	CPP *Bdnf* overexpression: LV-*Bdnf* LV-siR124a *Bdnf* knockdown: LV-miR124a	 ↓ ↓ ↑	Bahi and Dreyer 2013
Bdnf knockdown via viral-mediated down-regulation of miR124a in the DLS	Alcohol consumption (5% 2-BC) *Bdnf* overexpression: LV-BDNF LV-siR124a *Bdnf* knockdown: LV-miR124a	 ↓ ↓ ↑	
Bdnf knockdown via viral-mediated overexpression of miR-206 in the mPFC	Alcohol consumption (10% alcohol in operant self-administration)	↑	Tapocik et al. 2014
Bdnf knockdown via viral-mediated overexpression of miR-30a-5p in the mPFC	Alcohol consumption (IA2BC)	↑	Darcq et al. 2015
BDNF overexpression via miR-30a-5p inhibition in the mPFC (after 7 wk of IA2BC)	Alcohol consumption and preference (IA2BC)	↓	Darcq et al. 2015
BDNF infusion into the DLS of rat with a history of IA2BC	Alcohol consumption (20/10/2.5% alcohol in operant self-administration, 3 h after BDNF infusion)	-	Darcq et al. 2016
Viral-mediated p75NTR knockdown after 7 wk of IA2BC	Alcohol consumption (IA2BC, 4 wk after virus infection)	↓	Darcq et al. 2016
Intra-DLS infusion of LM11A-31 (p75NTR modulator) after 7 wk of IA2BC	Alcohol consumption (IA2BC, 2 h after LM11A-31 infusion)	↓	Darcq et al. 2016
Systemic administration of LM11A-31 after 7 wk of IA2BC	Alcohol consumption (IA2BC, 2 h after LM11A-31 administration)	↓	Darcq et al. 2016
Met68BDNF knockin mice	Alcohol consumption and preference (10% IA2BC) Alcohol consumption and preference (20% IA2BC) Alcohol + quinine consumption and preference (10% IA2BC) Alcohol + quinine consumption and preference (20% IA2BC)	- ↑ ↑ ↑	Warnault et al. 2016

Continued

Table 2. *Continued*

BDNF manipulation	Behavioral procedure	Effect	References
Viral-mediated overexpression of wild-type Val68BDNF in the vmPFC in Met68BDNF knockin mice	Alcohol consumption and preference (10% IA2BC + quinine, 5 d after infusion)	↓	Warnault et al. 2016
Systemic administration of the TrkB activator, LM22A-4 in Met68BDNF knockin mice	Alcohol consumption and preference (10% IA2BC + quinine, immediately after LM22A-4 administration)	↓	Warnault et al. 2016

(↑) increase, (↓) decrease.

(BDNF) Brain-derived neurotrophic factor, (2-BC) 2-bottle choice, (CPP) conditioned place preference, (DLS) dorsolateral striatum, (DMS) dorsomedial striatum, (NAc) nucleus accumbens, (ODNs) oligodeoxynucleotides, (PFC) prefrontal cortex, (mPFC) medial PFC, (LV) lentivirus, (IA2BC) intermittent access to 20% alcohol 2-bottle choice.

sion (Jeanblanc et al. 2013). Inhibition of the ERK1/2 pathway, prevented BDNF-induced decreases in alcohol self-administration, with no similar effects of PLCγ or PI3K inhibitors (Jeanblanc et al. 2013), suggesting that activation of the TrkB/ERK1/2 signaling pathway is necessary for the beneficial actions of BDNF on alcohol consumption. Moreover, the mRNA expression of preprodynorphin (Logrip et al. 2008) and dopamine D3 receptor (Jeanblanc et al. 2006) are increased following BDNF or Tat-RACK1 treatment, and inhibition of dopamine D3 receptor (Jeanblanc et al. 2006) or of dynorphin's receptor, the κ-opioid receptor (Logrip et al. 2008), reduced the ability of Tat-RACK1 to decrease alcohol consumption. Together, these data demonstrate that BDNF in the DLS gates alcohol intake via TrkB-mediated activation of ERK1/2 signaling, which results in the increase in the downstream effectors, preprodynorphin and dopamine receptor D3, which act to suppress alcohol intake (Logrip et al. 2015).

Interestingly, infusion of BDNF into the DLS of rats trained to chronically consume excessive levels of alcohol had no effects on alcohol consumption, suggesting that repeated cycles of access to high amounts of alcohol followed by withdrawal, preclude the ability of striatal BDNF to gate the level of alcohol self-administration (Darcq et al. 2016). The breakdown in BDNF signaling in the DLS is likely to be mediated through the reduction in the contribution of TrkB and the recruitment of p75NTR (Darcq et al. 2016), a low-affinity BDNF receptor, which counteracts the actions of TrkB (Kraemer et al. 2014). In support of this possibility, RNA-mediated knockdown of the p75NTR gene in the DLS, as well as intra-DLS infusion or systemic administration of the p75NTR modulator LM11A-31, reduced binge-like alcohol drinking (Darcq et al. 2016).

The beneficial actions of BDNF on alcohol intake are likely to also be mediated by additional brain regions. Specifically, amygdalar BDNF repressed both anxiety-like behavior and alcohol intake (Pandey et al. 2006), suggesting a function for BDNF in the amygdala in regulating anxiety-modulated alcohol consumption. Moreover, knockdown of BDNF expression via antisense oligonucleotide infusion in the MeA and CeA increased alcohol intake and anxiety-like behavior, which was reversed by BDNF infusion (Pandey et al. 2006). In the amygdala, BDNF likely reduces anxiety-like behavior and alcohol intake via increasing dendritic spine density (Moonat et al. 2011). A more recent study found that infusion of BDNF into the mPFC of alcohol-dependent mice decreased alcohol intake, and that viral-mediated overexpression of *Bdnf* in this brain region reduced drinking escalation in these mice (Haun et al. 2018).

Another mechanism for the breakdown in corticostriatal BDNF signaling involves miRNAs targeting BDNF. As mentioned above, excessive alcohol reduces *Bdnf* levels in the PFC via an miRNA-mediated mechanism in mice (Darcq et al. 2015) and rats (Tapocik et al.

2014). Overexpression of miR-206 in the mPFC of rats (Tapocik et al. 2014) or miR30a-5p in the mPFC of mice (Darcq et al. 2015) increased alcohol consumption. Conversely, intra-mPFC infusion of an inhibitor of miR30a-5p function led to a significant reduction in excessive alcohol drinking and preference (Darcq et al. 2015).

Finally, human and mouse studies suggest that innate malfunction of BDNF signaling may contribute to the development of AUD. Specifically, a loss-of-function mutation in BDNF in humans (G196A; also known as polymorphism rs6265) produces an amino acid substitution (Val66Met) leading to reduced activity-dependent release of BDNF (Egan et al. 2003; Chen et al. 2004). Human studies suggest that the Val66Met polymorphism increases the susceptibility to develop AUD. Specifically, carriers of the mutation are associated with earlier onset of alcoholism (Matsushita et al. 2004) and higher risk of relapse (Wojnar et al. 2009; Ron and Berger 2018). Transgenic mice expressing the mouse polymorphism (Val68/Met) exhibit compulsive-like alcohol consumption (Warnault et al. 2016). Overexpression of the WT BDNF in the mPFC of mutant Val68/MetBDNF mice rescues the excessive, compulsive alcohol-drinking phenotype (Warnault et al. 2016). Compulsive alcohol use in the Val68/MetBDNF knockin mice was also rescued by a systemic administration of the TrkB agonist, LM22A-4 (Warnault et al. 2016), suggestive of a potential therapeutic approach to treat humans carrying the Met66BDNF allele.

Summary—BDNF

In summary, the data presented here suggest that the corticostriatal BDNF pathway plays a crucial role in the regulation of alcohol consumption, keeping it in moderation via activation of the BDNF signaling within the DLS. In contrast, the transition from moderate-to-high intake results from the breakdown of the corticostriatal BDNF pathway. The mechanisms underlying the brain region selectivity of BDNF's beneficial actions on alcohol consumption should be addressed in future studies. Additionally, the identification of new drugs targeting BDNF or its downstream effectors may provide new leads for the treatment of AUD.

GDNF

GDNF is a secreted growth factor, initially identified in a glial-derived cell line (Lin et al. 1993). GDNF is expressed throughout the CNS during development, and in the adult brain the growth factor is highly expressed in the striatum, thalamus, cortex, and hippocampus (Pochon et al. 1997; Ortega-de San Luis and Pascual 2016). GDNF signals through the receptor tyrosine kinase RET (Durbec et al. 1996). Activation of RET by GDNF also requires the presence of the coreceptor GDNF-family receptor α1 (GFRα1) (Jing et al. 1996; Airaksinen and Saarma 2002). GDNF signaling depends on the presence of GFRα1 and RET in lipid raft compartments within the plasma membrane (Tansey et al. 2000; Paratcha et al. 2001; Tsui et al. 2015). Ligation of GDNF to RET and GFRα1 triggers the activation of several intracellular signaling cascades: the MAPK/ERK, PI3K, and PLCγ cascades (Airaksinen and Saarma 2002; Sariola and Saarma 2003). Interestingly, RET is highly expressed in the midbrain (Trupp et al. 1997; Glazner et al. 1998), whereas the distribution of GDNF and GFRα1 are much more widespread (Ortega-de San Luis and Pascual 2016). In brain regions deficient in RET, GDNF acts through alternate receptors, such as the adhesion proteins syndecan-3 (Bespalov et al. 2011) and the neuronal cell-adhesion molecule (NCAM) (Paratcha et al. 2003).

GDNF plays a vital role in neuron development (Airaksinen and Saarma 2002; Bespalov and Saarma 2007) and promotes axonal growth of hippocampal and cortical neurons by signaling through NCAM via a mechanism that is independent of RET (Paratcha et al. 2003). Postnatally, GDNF also regulates the activity of midbrain dopaminergic neurons. Specifically, GDNF is produced by striatal neurons (Pochon et al. 1997; Barroso-Chinea et al. 2005), and is retrogradely transported via dopaminergic neurons to the midbrain, namely, the SN (Tomac et al. 1995; Kordower et al. 2000) and VTA (Wang

et al. 2010), where the RET receptor is abundant (Trupp et al. 1997). Activation of GDNF signaling in the midbrain increases the spontaneous activity of dopaminergic neurons in both nigrostriatal and mesolimbic projections (Yang et al. 2001; Wang et al. 2010; Kumar et al. 2015), and infusion of GDNF into the VTA increases dopamine release in the NAc (Wang et al. 2010).

Given its regulatory effect on midbrain dopamine function, GDNF has been implicated as a potential treatment target to Parkinson's disease (Ibáñez and Andressoo 2017; Grondin et al. 2019). GDNF has also been suggested to be involved in several neuropsychiatric disorders in which the mesolimbic system plays an important role, including depression, anxiety, stress, and schizophrenia (Ibáñez and Andressoo 2017), and has been implicated as a key player in the regulation of intake of abused drugs (Carnicella and Ron 2009; Ghitza et al. 2010; Barak et al. 2019).

Alcohol Regulation of GDNF Expression

Studies in rodents indicate that *Gdnf* levels fluctuate in response to different regimens of alcohol exposure (see Table 3). For instance, 1 week of alcohol drinking in the IA2BC procedure (Carnicella et al. 2014), increased *Gdnf* mRNA levels in the VTA of rats when assessed at the end of the last 24-h drinking session, relative to water-drinking controls (Ahmadiantehrani et al. 2014). Similarly, a single systemic injection of a nonhypnotic dose of alcohol increased *Gdnf* mRNA expression in the VTA, with no effects on the NAc (Ahmadiantehrani et al. 2014). *Gdnf* expression in the VTA was still increased when measured immediately after a 30-min binge-like drinking session following 7 weeks of IA2BC training (Ahmadiantehrani et al. 2014). However, *Gdnf* levels in the VTA were down-regulated below the baseline of water-drinking controls in response to 7 weeks of IA2BC, when tested after a 24-h withdrawal period (Ahmadiantehrani et al. 2014). Together, these data suggest that *Gdnf* is an alcohol-responsive gene, which is up-regulated during short-term alcohol intake but down-regulated during withdrawal from excessive alcohol intake (Barak et al. 2019).

Notably, studies in humans reported elevated serum GDNF protein levels in individuals displaying mild-to-severe AUD (Lhullier et al.

Table 3. Effects of alcohol on GDNF expression

Treatment regimen	GDNF expression	Effect	References
Acute exposure (1.8 g/kg)	mRNA:		Ahmadiantehrani et al.
	VTA	↑	2014
	NAc	-	
	Protein:		
	VTA	↑	
Voluntary consumption (IA2BC), 1 wk	mRNA:		Ahmadiantehrani et al.
	VTA	↑	2014
	NAc	-	
Voluntary consumption (IA2BC), 7 wk	mRNA:		Ahmadiantehrani et al.
	VTA, NAc	-	2014
Voluntary consumption (IA2BC), 7 wk + 24 h deprivation	mRNA:		Ahmadiantehrani et al.
	VTA	↓	2014
	NAc	-	
Voluntary consumption (IA2BC), 7 wk + binge drinking	mRNA:		Ahmadiantehrani et al.
	VTA ("low drinkers")	↑	2014
	VTA ("excessive drinkers")	↑	

(↑) increase, (↓) decrease.

(GDNF) Glial cell line–derived neurotrophic factor, (mRNA) messenger RNA, (VTA) ventral tegmental area, (NAc) nucleus accumbens, (IA2BC) intermittent access to 20% alcohol 2-bottle choice.

2015), but reduced levels in alcohol-dependent individuals experiencing withdrawal (Heberlein et al. 2010), supporting the notion that the GDNF system is sensitive to voluntary alcohol intake, and that dysregulation of GDNF expression can be detected across species.

Mesolimbic GDNF and the Regulation of Alcohol Consumption

GDNF in the mesolimbic system plays a unique role in neuroadaptations underlying AUD (see Table 4). Specifically, infusion of recombinant GDNF into the rat VTA, an essential component of the brain reward circuitry (Volkow and Morales 2015), reduced lever pressing for alcohol (Carnicella et al. 2008). Moreover, intra-VTA infusion of GDNF also suppressed rat binge-like home cage alcohol intake, and the suppressive effects persisted 24 h and even 48 h after a single administration of the growth factor (Carnicella et al. 2009a; Barak et al. 2011a). Finally, intra-VTA infusion of GDNF also inhibited the postextinction reacquisition of operant alcohol self-administration, suggesting that the growth factor decreases relapse to alcohol consumption (Carnicella et al. 2008). Importantly, GDNF had no effect on the self-administration of sucrose (Carnicella et al. 2008), implying that the growth factor does not alter the general motivation to consume natural rewards.

GDNF was also shown to control the escalation in alcohol consumption in a chronic excessive alcohol-exposure protocol. Specifically, virus-mediated overexpression of GDNF in the NAc or VTA of rats blocked escalation from moderate-to-excessive alcohol drinking, as measured in the IA2BC procedure (Barak et al. 2015). Together, these data suggest that activation of the GDNF signaling pathway in the VTA

Table 4. Effects of GDNF-related manipulations on alcohol-related behaviors

GDNF manipulation	Behavioral procedure	Effect	References
Intra-VTA GDNF infusion (10 μg/ hemisphere)	Alcohol consumption (2-BC)	↓	Carnicella et al. 2009a; Barak et al. 2011a
	Operant self-administration	↓	Carnicella et al. 2008; Barak et al. 2011b
	Reacquisition of operant self-administration (relapse test)	↓	Carnicella et al. 2008
	CPP (acquisition)	↓	Barak et al. 2011b
	CPP (expression)	↓	Barak et al. 2011b
Viral-mediated GDNF overexpression	In the NAc or VTA:		Barak et al. 2015
	Escalation in alcohol consumption (IA2BC)	↓	
Viral-mediated GDNF knockdown	In the VTA:		Ahmadiantehrani et al. 2014
	Escalation in alcohol consumption (IA2BC)	↑	
	In the NAc:		Barak et al. 2015
	Escalation in alcohol consumption (IA2BC)	↑	
	Relapse after abstinence (IA2BC)	↑	
	Operant self-administration	↑	
	Reinstatement of operant self-administration (relapse test)	↑	
	Reacquisition of operant self-administration (relapse test)	↑	
GDNF or GFRα1 heterozygote knockout mice	Relapse after abstinence (2-BC)	↑	Carnicella et al. 2009b
	CPP	↑	

(↑) increase, (↓) decrease.

(GDNF) Glial cell line–derived neurotrophic factor, (VTA) ventral tegmental area, (2-BC) 2-bottle choice, (CPP) conditioned place preference, (NAc) nucleus accumbens, (IA2BC) intermittent access to 20% alcohol 2-bottle choice, (GFRα1) GDNF-family receptor α1.

produces a sustained reduction of alcohol-drinking behaviors.

To test the contribution of the endogenous GDNF system to alcohol-drinking phenotypes, GDNF expression in the VTA or NAc was knocked down by viral delivery of shRNA sequence targeting the *Gdnf* gene. Knockdown of *Gdnf* in either the VTA or NAc facilitated the escalation of IA2BC alcohol drinking compared to rats infected with a nonspecific control sequence in the same brain regions (Ahmadiantehrani et al. 2014; Barak et al. 2015). In line with these findings, GDNF heterozygote knockout (HET) mice, which show ∼50% reduction in GDNF protein expression (Griffin et al. 2006), consumed more alcohol than their WT littermates after a period of abstinence and exhibited increased alcohol-conditioned place preference (CPP), a measure of alcohol reward (Carnicella et al. 2009b). These findings could be linked to the observation that *Gdnf* HET mice exhibit higher levels of dopamine in the striatum (Airavaara et al. 2004). Taken together, these findings suggest that like BDNF, the endogenous GDNF system protects against the escalation to excessive alcohol drinking during the early stages of alcohol consumption, whereas long-term excessive alcohol exposure may lead to breakdown of this protective mechanism, resulting in the escalation of alcohol intake (Barak et al. 2019). Interestingly, reexposure to a context previously associated with nicotine decreased *Gdnf* expression in the VTA in 50%, and was associated with long-lasting (3 month) increases in operant alcohol self-administration and relapse (Zipori et al. 2017). These findings suggest that breakdown of the GDNF pathway in the mesolimbic system may provide a common neuroadaptation underlying the comorbidity of nicotine and alcohol abuse.

Findings also point out that the endogenous GDNF is differentially expressed in low and high alcohol drinkers. Specifically, although the IA2BC procedure generally produces a high number of excessively drinking rats (∼60%–70%), not all rats develop this typical pattern of alcohol consumption (Carnicella et al. 2014). Thus, alcohol-drinking rats can be segregated into two distinct groups: those whose alcohol intake progressively increases over time (high drinkers), and those who maintain moderate alcohol consumption (low drinkers). Interestingly, although binge-like alcohol drinking increased *Gdnf* expression in the VTA in both groups, the effect was considerably stronger among low drinkers (Ahmadiantehrani et al. 2014). Although this effect is confounded by the fact that excessive drinkers consumed higher levels of alcohol during the binge-drinking period (Ahmadiantehrani et al. 2014), these results suggest that GDNF is more responsive to alcohol and thus presumably more functional in low drinkers, compared to high drinkers. This conclusion was further supported by a negative correlation between alcohol intake levels and *Gdnf* expression in the VTA (Barak et al. 2015). Interestingly, these data are in line with data from human studies, indicating that serum GDNF is reduced in humans undergoing alcohol withdrawal (Heberlein et al. 2010), suggesting that low serum levels of GDNF may be an indicator of susceptibility to relapse. Taken together, these findings suggest that the sensitivity of the *GDNF* expression system to alcohol determines the profile of drinking. Thus, variation in the *GDNF* gene, particularly modifications that would impair the *GDNF* response to alcohol, should be investigated further as a possible marker of AUD susceptibility.

GDNF-dependent regulation of alcohol intake was shown to be mediated by the ERK1/2 pathway in the VTA (Carnicella et al. 2008). Specifically, intra-VTA infusion of GDNF activated ERK1/2 in the VTA, and specific inhibition of this signaling cascade but not of the PI3K pathway prevented GDNF-mediated suppression of alcohol self-administration (Carnicella et al. 2008). PLCγ inhibition in the VTA of rats reduced alcohol self-administration on its own, therefore it was impossible to conclude about the contribution of this pathway to the effects of GDNF on alcohol self-administration (Carnicella et al. 2008).

As described above, activation of GDNF signaling in the VTA produces a rapid increase in the spontaneous firing of VTA dopamine neurons (Wang et al. 2010), whereas withdrawal from alcohol reduces the activity of VTA neu-

rons (Diana et al. 1993; Bailey et al. 2001; Shen 2003; Shen et al. 2007; Barak et al. 2015). In line with the notion that GDNF reverses alcohol's actions in the mesolimbic system, infusion of GDNF into the VTA reverses the reduction in rat VTA dopamine firing (Barak et al. 2015). Furthermore, alcohol withdrawal reduces dopamine tone in the NAc (Weiss et al. 1996; Barak et al. 2011b), and intra-VTA administration of GDNF adjusted dopamine efflux in the NAc of rats undergoing a short period of withdrawal from heavy alcohol use (Barak et al. 2011b). Together, these results support the possibility that GDNF reduces alcohol intake by increasing VTA dopamine neuronal excitability, therefore reversing allostatic alterations in the mesolimbic dopamine system associated with withdrawal from long-term consumption of high alcohol levels (Barak et al. 2019).

Although GDNF triggers dopamine release in the NAc (Wang et al. 2010; Barak et al. 2011a), GDNF itself is not rewarding (Barak et al. 2011a); therefore, it does not reduce alcohol consumption by substituting for alcohol reward. Specifically, intra-VTA infusion of GDNF did not lead to the expression of alcohol-CPP (Barak et al. 2011a), confirming that the growth factor is not rewarding. Furthermore, intra-VTA GDNF infusion disrupted both the acquisition and the expression of alcohol-CPP (Barak et al. 2011a), suggesting that the growth factor suppresses the reinforcing effects of alcohol, rather than generating reinforcing effects on its own. Finally, infusion of GDNF into the VTA also produced a downward shift in the dose–response curve for alcohol self-administration (Barak et al. 2011a), indicating that this growth factor does not substitute for or augment the rewarding effects of alcohol, but rather suppresses the motivation for alcohol seeking and drinking.

It is important to note that while the effects of GDNF on alcohol drinking are rapid, they persist for a long time (Carnicella et al. 2009a; Barak et al. 2019). It has been suggested that these long-term effects occur through an autoregulatory cycle, in which the binding of GDNF to its receptor induces GDNF expression (He and Ron 2006). Specifically, GDNF treatment of the dopaminergic-like SH-SY5Y cell line induced long-lasting increases in the growth factor's levels, resulting in long-lasting activation of RET (He and Ron 2006). Furthermore, this autoregulatory positive feedback loop was also observed in vivo, as infusion of recombinant GDNF into the VTA of rats increased the expression of GDNF mRNA and protein for at least 48 h (Barak et al. 2011a). This long-term up-regulation of *Gdnf* mRNA expression was prevented by inhibition of protein synthesis, as well as by the down-regulation of *Gdnf* mRNA (Barak et al. 2011a). Together, these findings indicate that GDNF positively regulates its own expression, and that this process depends on de novo transcription and translation of the growth factor. The relevance of this autoregulatory loop was further demonstrated for alcohol intake, as the long-lasting attenuation of alcohol consumption by intra-VTA GDNF infusion was prevented by down-regulation of *Gdnf* mRNA levels in the VTA, as well as by inhibition of protein synthesis (Barak et al. 2011a). Together, these findings suggest that long-lasting suppression of alcohol consumption is mediated at least in part through an autoregulatory loop in which GDNF promotes its own expression and signaling.

Summary—GDNF

Because animal studies show that GDNF affects alcohol-drinking behaviors, and human studies found abnormal levels of GDNF in AUD patients (Heberlein et al. 2010; Lhullier et al. 2015), targeting GDNF signaling may provide a promising approach for the development of new drugs to treat AUD. A promising pharmacological approach is to suppress alcohol consumption via a GDNF message-inducer, which increases the endogenous levels of GDNF. This approach is expected to induce a long-lasting activation of GDNF signaling, as a result of the positive feedback loop of the growth factor (Barak et al. 2011a). Interestingly, the Food and Drug Administration (FDA)-approved drug cabergoline, was shown to increase the expression of *GDNF* in dopaminergic-like SH-SY5Y cells, resulting in activation of the downstream signaling pathway (Carnicella et al. 2009c). Systemic

administration of a single dose of cabergoline suppressed alcohol consumption in rodents via a GDNF-dependent mechanism (Carnicella et al. 2009c). Therefore, drugs like cabergoline, mimicking GDNF, can be potential pharmacotherapy to suppress excessive alcohol drinking and relapse.

FGF2

FGF2 is a member of the FGF family, consisting of 22 members (Chlebova et al. 2009; Förthmann et al. 2015). FGF2 is highly abundant throughout the neuronal tube from the early stages of embryonic development (Dono et al. 1998; Ford-Perriss et al. 2001). FGF2 has been extensively studied for its role during development—in cell proliferation, differentiation, growth, survival, and angiogenesis (Dono et al. 1998; Ford-Perriss et al. 2001; Reuss and von Bohlen und Halbach 2003). In adulthood, FGF2 is expressed in both neurons and astrocytes (Gonzalez et al. 1995; Reuss and von Bohlen und Halbach 2003) in multiple brain regions, including the frontal cortex, thalamus, hypothalamus, striatum, hippocampus, amygdala, ventral midbrain (SN and VTA), and pons (Gonzalez et al. 1995; Reuss and von Bohlen und Halbach 2003). In adulthood, FGF2 has been implicated in learning and memory processes (Graham and Richardson 2011).

FGF2 binds to FGF receptor 1 (FGFR1), a receptor tyrosine kinase (Ford-Perriss et al. 2001). The binding of FGF2 to this receptor leads to receptor dimerization and to the activation of the receptor via autophosphorylation (Eswarakumar et al. 2005), resulting in the activation of the PLCγ, ERK1/2, and PI3K signaling (Numakawa et al. 2002; Reuss and von Bohlen und Halbach 2003; Eswarakumar et al. 2005; Peltier et al. 2007).

Malfunctioning of FGF2 signaling has been implicated in numerous neuropsychiatric disorders, including anxiety (Perez et al. 2009; Eren-Koçak et al. 2011; Turner et al. 2012), depression (Mallei et al. 2002; Maragnoli et al. 2004; Riva et al. 2005; Elsayed et al. 2012; Turner et al. 2012), stress-related disorders (Molteni et al. 2001a,b; Fumagalli et al. 2005; Xia et al. 2013), and schizophrenia (Klejbor et al. 2006; van Scheltinga et al. 2010), as well as in neurodegenerative diseases (Cummings et al. 1993; Claus et al. 2004; Timmer et al. 2007; Kiyota et al. 2011). In addition, accumulating evidence suggests that FGF2 is involved in the behavioral and neurobiological effects of drugs of abuse, including cocaine, amphetamine, and nicotine (Even-Chen and Barak 2019a).

Alcohol Regulation of FGF2 Expression

An acute alcohol injection (2.5 g/kg) increased the mRNA expression of *Fgf2* levels in the mouse dorsal striatum, NAc, and dorsal hippocampus (Even-Chen et al. 2017). Longer alcohol exposure (2.5 g/kg injection once a day for 7 days) limited these changes to the dorsal striatum at both its subregions, the DMS and the DLS, and these increases were found to be mediated by dopamine D2-like receptor activation (Even-Chen et al. 2017). The same 7-day exposure also up-regulated the mRNA expression of FGF2 receptor, *Fgfr1,* in the dorsal striatum and dorsal hippocampus (Even-Chen and Barak 2019b). Furthermore, voluntary consumption of 20% alcohol for 5–7 weeks increased *Fgf2* and *Fgfr1* expression in the DMS, but not the DLS, of both mice and rats (Even-Chen et al. 2017; Even-Chen and Barak 2019b). Thus, although limited noncontingent exposure to alcohol leads to widespread increases in mesolimbic *Fgf2/Fgfr1* expression, it seems that extended and/or voluntary alcohol consumption results in more spatially specific effects on the expression of the growth factor and its receptor (see Table 5 for a summary of the effects of alcohol on brain FGF2 expression).

FGF2 and the Regulation of Alcohol Consumption

Systemic administration of recombinant FGF2 to mice increases alcohol intake and preference, with no similar effects on the consumption of water or natural rewards (sweetened solution: sucrose or saccharin) (Even-Chen et al. 2017). Moreover, infusion of recombinant FGF2 into the DMS of rats increased alcohol consumption

Table 5. Effects of alcohol on FGF2 expression

Treatment regimen	FGF2 expression	Effect	References
Acute exposure (2.5 g/kg)	mRNA:		Even-Chen et al. 2017
	Dorsal striatum, NAc, and hippocampus	↑	
Subchronic exposure (7 × 2.5 g/kg)	mRNA:		Even-Chen et al. 2017
	DMS and DLS	↑	
Voluntary consumption (IA2BC)	mRNA:		Even-Chen et al. 2017
	DMS	↑	
Sucrose operant self-administration	Protein:		Hafenbreidel et al. 2015
	Infralimbic PFC (after 9 withdrawal days)	-	

(↑) increase, (↓) decrease.

(FGF2) Fibroblast growth factor 2, (mRNA) messenger RNA, (NAc) nucleus accumbens, (DMS) dorsomedial striatum, (DLS) dorsolateral striatum, (IA2BC) intermittent access to 20% alcohol 2-bottle choice, (PFC) prefrontal cortex.

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and preference. Inhibition of the PI3K, but not of the ERK1/2 signaling in the DMS, blocked the effects of FGF2 on alcohol intake and preference (Even-Chen and Barak 2019b), indicating that the effects of FGF2 are mediated, at least in part, via the PI3K pathway in the DMS.

In contrast, blocking FGF2 activity in the DMS with an anti-FGF2-neutralizing antibody suppressed alcohol intake and preference (Even-Chen et al. 2017). Likewise, systemic administration of the FGFR1 inhibitor PD173074 to mice, as well as its infusion into the DMS of rats, decreased alcohol consumption and preference, with no effects on natural reward consumption (Even-Chen and Barak 2019b). Together, these data indicate that increasing the activity of FGF2-FGFR1 increases alcohol intake, where inhibition of the growth factor's activity reduces alcohol intake (see Table 6 for a summary of the effects of FGF2-related manipulations on alcohol-drinking behaviors).

Summary—FGF2

Taken together, these data suggest that FGF2 acts as a positive regulator of alcohol consumption and forms a positive feedback loop centered in the DMS, in which alcohol increases FGF2 levels, and FGF2, in turn, increases the consumption of alcohol. Although additional studies are required, it seems that inhibition of FGF2 production and/or its receptor's activity could be used to reduce alcohol consumption, providing a potential therapeutic target.

MIDKINE, PLEIOTROPHIN, AND ALK

The growth factors MDK and PTN (Wellstein 2012) bind to and activate the receptor tyrosine kinase ALK (Hallberg and Palmer 2016). Both MDK and PTN promote growth, survival, differentiation, and recovery of neurons (Herradón and Pérez-García 2014), and MDK was shown to promote the outgrowth of neurons and to inhibit neuronal apoptosis by activation of the PI3K and ERK1/2 pathways (Owada et al. 1999). High expression of ALK and its ligands was identified in the developing mouse central nervous system (CNS) (Morris et al. 1997). The growth factors and their receptor are also expressed, albeit to a lesser extent, in the adult mouse brain (Morris et al. 1997). *Alk* mRNA is almost exclusively expressed in the midbrain, thalamus, and olfactory bulb of embryonic and neonatal mice (Iwahara et al. 1997). ALK has been implicated in the pathogenesis of several types of cancer (Hallberg and Palmer 2013). In addition, the expression levels of brain MDK and PTN has been associated with drugs of abuse (Herradón and Pérez-García 2014).

Alcohol Regulation of MDK/PTN Expression

Only a few studies examined the effects of alcohol on MDK and PTN expression (Table 7). An acute alcohol injection (2 g/kg i.p.) was reported to induce increases of ∼25% and ∼50% in *Ptn* mRNA and PTN protein levels in the PFC, re-

Table 6. Effects of FGF2-related manipulations on alcohol-related behaviors

FGF2 manipulation	Behavioral procedure	Effect	References
Systemic FGF2 injection (80 μg/kg)	Alcohol consumption and preference (IA2BC)	↑	Even-Chen et al. 2017
	Total fluids consumption	-	
Intra-DMS FGF2 infusion (200 ng/hemisphere)	Alcohol consumption and preference (IA2BC)	↑	Even-Chen et al. 2017; Even-Chen and Barak 2019b
	Total fluids consumption	-	
Anti-FGF2-neutralizing antibody in the DMS	Alcohol consumption and preference (IA2BC)	↓	Even-Chen et al. 2017; Even-Chen and Barak 2019b
	Total fluids consumption	-	
Systemic FGFR1 antagonist	Alcohol consumption and preference (IA2BC)	↓	Even-Chen and Barak 2019b
	Total fluids consumption	-	
Intra-DMS FGF2 antagonist	Alcohol consumption and preference (IA2BC)	↓	Even-Chen and Barak 2019b
	Total fluids consumption	-	
Systemic FGF2 injection (80 μg/kg)	Sucrose and saccharin consumption and preference (2-BC)	-	Even-Chen et al. 2017

(↑) increase, (↓) decrease.
(FGF2) Fibroblast growth factor 2, (IA2BC) intermittent access to 20% alcohol 2-bottle choice, (DMS) dorsomedial striatum, (FGFR1) FGF receptor 1, (2-BC) 2-bottle choice.

spectively (Vicente-Rodríguez et al. 2014b). In humans, increases in the mRNA and protein expression of MDK was found in the NAc and PFC tissues of AUD patients (Flatscher-Bader et al. 2005; Flatscher-Bader and Wilce 2006, 2008).

Regulation of Alcohol-Related Behaviors by MDK/PTN/ALK

The first evidence for the causal role of ALK in alcohol-related behaviors came from the finding that a loss-of-function mutation in ALK resulted in lower sensitivity of fruit flies to the acute sedating effect of alcohol (Lasek et al. 2011). Similarly, *Alk* knockout mice showed higher loss of righting reflex (LORR), also pointing to higher sensitivity to alcohol (Lasek et al. 2011). *Alk* knockout mice were also reported to consume more alcohol in a binge-like drinking test (Lasek et al. 2011; Schweitzer et al. 2016) and in operant alcohol self-administration (Mangieri et al. 2017) compared to WT mice. *Alk* knockout mice did not differ in the escalation of alcohol drinking after preexposure to alcohol in an intermittent alcohol vapor regimen (Schweitzer et al. 2016).

In contrast to the findings with *Alk* knockout mice, infection of the VTA of mice with viral-delivered shRNA targeting *Alk* reduced drinking in a 4-day alcohol DID test, compared to the control scrambled shRNA (Dutton et al. 2017). Similarly, the ALK inhibitors NVP-TAE684 or alectinib, reduced alcohol consumption in the binge-like drinking test, with no similar effect on sucrose drinking (Dutton et al. 2017). In addition, NVP-TAE684 treatment prevented the acquisition of alcohol-CPP (Dutton et al. 2017). The authors suggested that the opposite effects on alcohol drinking between *Alk* knockout mice and the treatment with the ALK inhibitors or local knockdown of the gene,

Table 7. Effects of alcohol on ALK expression

Treatment regimen	ALK expression	Effect	References
Acute alcohol injection (2 g/kg i.p.)	mRNA: PFC	↑	Vicente-Rodríguez et al. 2014b
	Protein: PFC	↑	

(↑) increase, (↓) decrease.
(ALK) Anaplastic lymphoma kinase, (mRNA) messenger RNA, (PFC) prefrontal cortex.

Table 8. Effects of ALK-related manipulations on alcohol-related behaviors

ALK manipulation	Behavioral procedure	Effect	References
Alk$^{-/-}$ mice	Alcohol consumption (DID)	↑	Lasek et al. 2011
	LORR test	↑	
Alk$^{-/-}$ mice	Operant alcohol self-administration	↑	Mangieri et al. 2017
Alk$^{-/-}$ mice	Alcohol consumption (2-BC) followed by chronic intermittent exposure	-	Schweitzer et al. 2016
ALK inhibitors	Binge-like alcohol consumption	↓	Dutton et al. 2017
	CPP	↓	
Viral-mediated down-regulation of *Alk* in VTA	Binge-like alcohol consumption	↓	
Mdk$^{-/-}$ mice	CPP	↑	Vicente-Rodríguez et al. 2014a
	Rotarod test	↓	
	LORR test	↓	
Mdk$^{-/-}$ mice	Alcohol consumption (2-BC)	↑	Chen et al. 2017
	Binge-like alcohol consumption	↑	
Viral-mediated down-regulation of *Mdk* in the VTA	Binge-like alcohol consumption	↑	
Ptn$^{-/-}$ mice	CPP	↑	Fernández-Calle et al. 2019
Ptn$^{-/-}$ mice	CPP	↑	Vicente-Rodríguez et al. 2014b
	LORR test	-	
	Rotarod test	↑	
Cortex- and hippocampus-specific *Ptn* overexpression (*Ptn*-Tg mice)	CPP	↓	
	LORR test	↓	
	Rotarod test	↑	

(↑) increase, (↓) decrease.

(ALK) Anaplastic lymphoma kinase, (DID) drinking in the dark, (LORR) loss of righting reflex, (2-BC) 2-bottle choice, (CPP) conditioned place preference, (VTA) ventral tegmental area.

may be a result of compensatory mechanisms in *Alk* knockout mice, which have global lower levels of ALK throughout embryonic development.

Similar to the results obtained with ALK manipulations, MDK and PTN were found to affect alcohol-related behaviors in animal models as well. Specifically, *Mdk* knockout mice consume less alcohol than WT controls, but the acquisition of alcohol-CPP was enhanced in *Mdk* knockout mice (Vicente-Rodríguez et al. 2014a). In addition, *Mdk* knockout mice showed delayed recovery from alcohol-induced ataxia, with no effect on LORR (Vicente-Rodríguez et al. 2014a). Down-regulation of MDK by viral-mediated delivery of shRNA in the VTA of mice also reduced alcohol consumption (Chen et al. 2017). Similar behavioral phenotypes were detected with *Ptn* knockout mice, which showed a stronger acquisition of alcohol-CPP compared to WT controls (Vicente-Rodríguez et al. 2014b; Fernández-Calle et al. 2019). In contrast, alcohol-CPP was abolished in the Ptn transgenic (PTN-Tg) mice, in which *Ptn* is overexpressed in the cortex and hippocampus (Vicente-Rodríguez et al. 2014a). Both *Ptn* knockout and overexpressing mice showed reduced motor coordination in the rotarod test, and Ptn overexpressing mice showed longer time to recover in the LORR test (Vicente-Rodríguez et al. 2014a). Table 8 summarizes the effects of ALK-related manipulations on alcohol-related behaviors.

Summary—Midkine, Pleiotrop, and ALK

More data are required to clarify the role of the PTN and MDK in alcohol-related behaviors. The recent data indicating that genetic down-regulation of ALK reduces alcohol drinking, and that ALK inhibitors are also suppressors of alcohol consumption in animal models, sug-

gest that ALK may provide a promising therapeutic target, although further research is needed to better characterize its potential.

IGF-1

IGF-1 is a 70–amino acid polypeptide hormone, structurally similar to insulin (Laron 2001). IGF-1 has been implicated in cell growth and survival, differentiation, proliferation, and maturation (Delafontaine et al. 2004). The expression of this growth factor is high mainly through developmental stages, and then slowly declines with age (Junnila et al. 2013). Its synthesis and secretion are mainly regulated by nutrient intake (Breese et al. 1991) and pituitary secretion of growth hormone (GH) (Clemmons 2004). After secretion, IGF-1 binds to IGF-1 receptor (IGF-1R), a membrane-bound receptor tyrosine kinase. To establish the interaction between IGF-1 and its receptor, IGF-1 binds with high affinity to IGF-1-binding proteins (IGFBPs), present extracellularly (Allard and Duan 2018). Ligation of IGF-1 with IGF-1R activates the ERK1/2 and PI3K signaling pathways (Wrigley et al. 2017). While IGF-1 is primarily synthesized in the liver, it is also synthesized locally in almost every other organ, including brain regions related to neurogenesis, the olfactory bulb, cerebellum, and hippocampus (Wrigley et al. 2017).

Alcohol Regulation of IGF-1 Expression

Studies in rodents indicated alcohol-related changes of *Igf1* mRNA expression and IGF-1 protein levels in the brain (Table 9). For example, chronic alcohol liquid diet (36% alcohol for 6 wk) reduced the mRNA expression levels of *Igf-1* in the temporal lobe (Cohen et al. 2007). In addition, IGF-1 protein levels were reduced in the hippocampus 48 h after binge-like alcohol exposure (oral gavage) in male and female rats, and 4 days of binge-like exposure reduced IGF-1 protein levels only in female rats (Maynard et al. 2018). Prenatal alcohol exposure of dams yielded higher whole brain *Igf-1* mRNA levels in the exposed offspring (Breese et al. 1994). In contrast, two other studies demonstrated that chronic prenatal exposure reduced *Igf-1* mRNA expression levels in the whole rat brain (Singh et al. 1996), and in the cerebellum (Soscia et al. 2006), with no change in the cerebellum in another study (de la Monte et al. 2005). Postnatal injections of alcohol to pups yielded no change in IGF-1 expression in the cerebellum, but elevated IGF-1R protein levels (Ewenczyk et al. 2012). Together, these findings suggest that IGF-1 levels are altered by alcohol exposure; however, more studies are required to better characterize these effects of alcohol on brain IGF-1 in adulthood, particularly after voluntary alcohol drinking.

Table 9. Effects of alcohol on IGF-1 expression

Treatment regimen	IGF-1 expression	Effect	References
Liquid diet (37% for 6 wk)	mRNA:		Cohen et al. 2007
	Temporal lobe	↓	
Oral gavage (5 mg/kg 3 times/day for 4 d)	Protein:		Maynard et al. 2018
	Hippocampus	↓	
Postnatal exposure (i.p injections 2 mg/kg/day on PND 2–8)	mRNA:		Ewenczyk et al. 2012
	Cerebellum	-	
Chronic prenatal exposure	mRNA:		Soscia et al. 2006
	Cerebellum	↓	
Chronic prenatal exposure	mRNA:		de la Monte et al. 2005
	Cerebellum	-	
Chronic prenatal exposure	mRNA:		Singh et al. 1996
	Whole brain	↓	
Chronic prenatal exposure	mRNA:		Breese et al. 1994
	Whole brain	↑	

(↑) increase, (↓) decrease.
(IGF-1) Insulin-like growth factor 1, (mRNA) messenger RNA, (PND) postnatal day.

Table 10. Effects of IGF-1-related manipulations on alcohol-related behaviors

IGF-1 manipulation	Behavioral procedure	Effect	Reference
Intranasal delivery of IGF-1 in postnatal rats	Alcohol-induced locomotor activity	-	McGough et al. 2009
	Alcohol-induced motor coordination	↓	
	Alcohol-related Morris water maze spatial learning	-	

(↑) increase, (↓) decrease.
(IGF-1) Insulin-like growth factor 1.

Interestingly, the effects of alcohol on IGF-1 expression were also studied in healthy humans, as well as in individuals with AUD. Specifically, IGF-1 serum levels declined slightly 6 h, whereas IGFBP-1 were increased 2 h, after alcohol exposure in healthy humans (Röjdmark et al. 2000). Another study detected increases in IGFBP-1 levels, but no changes in IGF-1 serum levels in healthy individuals after alcohol exposure (Röjdmark et al. 2001). Moreover, the level of *Igf1* mRNA was reduced in the cerebellum of AUD patients (de la Monte et al. 2005). In line with this finding, IGF-1 serum levels were found to be reduced in individuals with AUD, compared to healthy individuals (Röjdmark and Brismar 2001; Leggio et al. 2008), even after protracted withdrawal (García-Marchena et al. 2017). Taken together, both animal and human studies point to deficient expression of IGF-1 following alcohol exposure.

Regulation of Alcohol-Related Behaviors by IGF-1

Using the parallel bar motor coordination test, it was demonstrated that intranasal delivery of IGF-1 on PND 10–13 reversed the impairing effects of neonatal alcohol exposure on motor coordination, but had no effects on abnormalities caused by alcohol exposure in spatial learning (as measured in the Morris water maze) and locomotor activity in rats (McGough et al. 2009). These findings suggest that IGF-1 may have potential beneficial effects against some of the early life harmful effects of alcohol exposure (see Table 10 for summary).

Summary—IGF-1

In summary, while some data indicate that IGF-1 might interact with alcohol exposure, and that IGF-1 treatment may have beneficial effects in preventing the effects of alcohol, additional studies are required to establish the involvement of IGF-1 in alcohol-drinking behaviors and in AUD. Giving that IGF-1 was shown to cross the blood–brain barrier (Reinhardt and Bondy 1994), systemic administration of human IGF-1 replacement therapies, may provide promising candidates in further explorations for AUD treatment. Thus, extensive research on the effects of IGF-1 on alcohol-related behaviors is needed.

GENERAL SUMMARY AND CONCLUDING REMARKS

We survey here the literature regarding the involvement of several growth factor systems in alcohol in AUD. We focused on two directions of the alcohol–growth factor interaction: the effects of alcohol on the expression of the growth factors (or their receptors), and regulation of alcohol-related behaviors by manipulations on the growth factor systems. While the reports are not always consistent, several conclusions can be drawn from this review.

We previously classified the molecular mechanisms that control alcohol-drinking behaviors into two clusters (Ron and Barak 2016). Specifically, we termed the signaling pathways that contribute to the transition from moderate-to-excessive alcohol consumption as "GO pathways," whereas the molecular pathways that promote resilience against escalation

of alcohol consumption and keep alcohol intake in moderation, as the "STOP pathways" (Ron and Barak 2016; Ron and Berger 2018). In the context of this classification, we can roughly sort the growth factors that we reviewed here into these two categories. Growth factors that belong to "STOP pathways" include GDNF in the mesolimbic systems (Barak et al. 2019) and BDNF in the corticostriatal system (Logrip et al. 2015). These growth factors belong in the "STOP pathways" category as activation of these systems suppress alcohol drinking. On the contrary, striatal FGF2 has been suggested to be a part of the "GO pathway," because elevation in the striatal levels of this growth factor were shown to increase alcohol intake, and its inactivation suppresses drinking (Even-Chen et al. 2017; Even-Chen and Barak 2019a,b). The classification of MDK/PTN/ALK is less clear because of the conflicting findings described above. However, the recent finding that specific viral-mediated down-regulation of *Alk*, as well as its pharmacological inhibition, reduces drinking (Dutton et al. 2017) and strengthens the possibility that ALK plays a role in the "GO pathways." Finally, because of the paucity of information from the studies assessing the effects of IGF-1 manipulations on alcohol-related behaviors, it is not possible yet to determine the role of this growth factor in the regulation of alcohol intake.

It is interesting to note that all the growth factors we mention here activate receptor tyrosine kinases, which in turn activate similar downstream intracellular signaling pathways (e.g., ERK1/2, PI3K, and PLCγ). Although it could be expected that activation of similar signaling pathways would yield similar phenotypes, the data reviewed here shows diverse outcomes, suggesting that additional factors determine the effects of the growth factor on alcohol-drinking behaviors. For example, activation of the MAPK pathway in the VTA by GDNF (Carnicella et al. 2008) or in the DLS by BDNF (Jeanblanc et al. 2013) reduces alcohol intake. In contrast, activation of the PI3K-AKT pathway in the NAc (Neasta et al. 2011), or in the DMS by FGF2 (Even-Chen and Barak 2019b), mediates increased alcohol consumption. As we previously suggested (Ron and Barak 2016), it is most likely that the phenotype is determined by complex interaction between the site of action and the specific signaling pathway that mediates the behavioral effects.

Finally, the translational implications of findings from animal studies for AUD in humans is a critical question. While we do not systematically review here studies that implicate alteration in growth factors in human patients, we mentioned several findings that clearly link fluctuations in the growth factors to the severity of AUD. We also touched upon the possibility that genetic variations in growth factors in humans is a predisposition factor for the development of the disease. In addition, drugs that interfere with or activate some of the growth factor systems have been reported to yield promising outcomes in animal models. Therefore, further research is required to fully understand the translational value of these reports, including translation of the findings in animal models to clinical trials in human patients.

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