Cellular and Molecular Neurobiology (2019) 39:721–727
https://doi.org/10.1007/s10571-019-00681-9

REVIEW PAPER

VGF has Roles in the Pathogenesis of Major Depressive Disorder and Schizophrenia: Evidence from Transgenic Mouse Models

Takahiro Mizoguchi[1] · **Hideaki Hara**[1] · **Masamitsu Shimazawa**[1]

Received: 21 January 2019 / Accepted: 25 April 2019 / Published online: 29 April 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Mental disorders, such as major depressive disorder and schizophrenia, are complex multigenetic conditions, but focused studies of single genes might reveal genes involved in the pathogenesis of mental disorders, including major depressive disorder and schizophrenia. Several candidate genes have been identified using transgenic mice. VGF nerve growth factor inducible (VGF) is a neuropeptide expression of which is induced by nerve growth factor (NGF). VGF is robustly and exclusively synthesized in neuronal and neuroendocrine cells. In central nervous system (CNS), VGF is extensively expressed especially in the cerebral cortex, hippocampus, and hypothalamus. VGF has many roles in the CNS, such as promotion of synaptic plasticity, neurogenesis, and neurite outgrowth. In clinical studies, altered expression and genetic mutations of VGF have been reported in patients with major depressive disorder and schizophrenia. On this basis, studies using transgenic mice to overexpress or knockout VGF have been performed to investigate the roles of upregulation or downregulation of VGF. In this review, we will discuss studies of the roles of VGF using transgenic mice and its relevance to pathologies in major depressive disorder and schizophrenia.

Keywords Central nervous system · VGF nerve growth factor inducible · Transgenic mice · Major depressive disorder · Schizophrenia

Introduction

VGF nerve growth factor inducible (VGF) was first identified as a neuropeptide expression of which is induced by nerve growth factor (NGF) (Levi et al. 1985). VGF expression is also induced by several other growth factors, such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) (Bonni et al. 1995). VGF promotes phosphorylation of tropomyosin receptor kinase B (TrkB) and its downstream factors, including Erk and CREB (Jiang et al. 2018c; Lin et al. 2015). Thus, it is conjectured that VGF is involved in a VGF/BDNF/TrkB autoregulatory loop (Jiang et al. 2018c; Lin et al. 2015).

VGF is a 68 kDa polypeptide consisting of 615 (human) or 617 (mouse and rat) amino acids with a typical secretory leader sequence of 22 amino acids at the N-terminal, which promotes translocation to the endoplasmic reticulum (Ferri et al. 2011). VGF and VGF-derived peptides are located in large dense core vesicles (LDCVs) and are released through a secretory pathway in response to depolarizing signals (Benson and Salton 1996; Laslop et al. 1994; Salton et al. 1991). Moreover, VGF has been implicated in the formation of LDCVs in peripheral tissues (Fargali et al. 2015; Stephens et al. 2017). VGF is robustly and exclusively synthesized in neuronal and neuroendocrine cells (Levi et al. 1985; Salton et al. 1991; Snyder et al. 1998; van den Pol et al. 1994). VGF is cleaved by prohormone convertases (PC) 1/3 and PC2 into TLQP-21, AQEE-30, LQEQ-19, TLQP-62, and neuroendocrine regulatory peptide-1 and -2 (NERP-1 and -2) (Possenti et al. 1989; van den Pol et al. 1994; Yamaguchi et al. 2007). In peripheral tissues, VGF is expressed in the pituitary, adrenal medulla, gut, and pancreas (Ferri et al. 1992). On the other hand, VGF is expressed extensively in central nervous system (CNS), especially in the cerebral cortex, hippocampus, and hypothalamus (van den Pol et al. 1994; Snyder and Salton 1998). Several studies revealed that VGF-derived peptides has many functions in CNS and peripheral tissues. TLQP-62 and AQEE-30 enhanced synaptic activity in the

---

✉ Masamitsu Shimazawa
shimazawa@gifu-pu.ac.jp

[1] Molecular Pharmacology, Department of Biofunctional Evaluation, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan

hippocampal neurons (Alder et al. 2003), whereas TLQP-21, AQEE-30, and LQEQ-19 have neuroprotective effects in several conditions (Noda et al. 2015, 2019; Severini et al. 2008; Takeuchi et al. 2018). Moreover, TLQP-21, AQEE-30, and TLQP-62 promoted insulin secretion (Petrocchi-Passeri et al. 2015; Stephens et al. 2012). In clinical studies, changes in the expression of VGF have been reported in patients with major depressive disorder and schizophrenia (Cattaneo et al. 2010b; Jiang et al. 2017; Huang et al. 2006, 2007). On this basis, studies using germline VGF knockout mice, αCamk2-Cre/+; *Vgf*$^{\text{flpflox/flpflox}}$ mice, synapsin-Cre/+; *Vgf*$^{\text{flpflox/flpflox}}$ mice, and VGF-overexpressing mice have been performed to investigate the roles of upregulation and/or downregulation of VGF (Mizoguchi et al. 2017, 2018; Jiang et al. 2018b; Ellis et al. 2017; Bozdagi et al. 2008; Hunsberger et al. 2007). In addition, the influence of regional upregulation and downregulation of VGF has been investigated with adeno-associated virus (AAV)-VGF-injected wild-type mice and AAV-CreGFP-injected *Vgf*$^{\text{flpflox/flpflox}}$ mice (Jiang et al. 2018b).

In this review, we discuss the roles of VGF in the pathology of major depressive disorder and schizophrenia based on evidence from studies of transgenic mice.

VGF-Related Expression and Genomic Changes in Patients with Major Depressive Disorder and Schizophrenia

Only a few studies have previously reported that there are changes in VGF expression and the VGF genomic locus associated with major depressive disorder and schizophrenia. In patients with major depressive disorder who are drug free for at least 2 weeks, *VGF* mRNA levels were significantly reduced to approximately half in leukocytes compared with healthy subjects (Cattaneo et al. 2010b). This reduction was rescued at the level of healthy subjects after 12 weeks of treatment with escitalopram (Cattaneo et al. 2010b). In addition to VGF, BDNF was also decreased in the same depressive patients, and restored to normal levels following 12 weeks of escitalopram treatment (Cattaneo et al. 2010a). Interestingly, a positive association was found between the changes of two proteins induced by the treatment ($r = 0.557$, $P = 0.012$) (Cattaneo et al. 2010b). Another study reported that *VGF* mRNA in depressed patients was decreased, and antidepressant treatment significantly increased *VGF* mRNA only in responders (Cattaneo et al. 2013). In addition to *VGF* mRNA levels in leukocyte, VGF protein concentrations in major depressive disorder patients were lower compared to healthy controls, and rescued by the treatment of antidepressant, including escitalopram and duloxetine [mean ± SD, control: 1273.77 ± 229.36, pretreatment: 1078.29 ± 201.54, posttreatment: 1441.68 ± 360.47 (pg/ml)] (Jiang et al. 2017). Other several reports indicate that the VGF levels in serum and prefrontal cortex were also decreased in patients with major depressive disorder (Jiang et al. 2018a; Chen et al. 2018). Only one study reported that the expression level of VGF is increased in cerebrospinal fluid of patients with major depressive disorder, although it is necessary to consider the effect of medication (Huang et al. 2006). In addition to expression changes, a positive correlation between two VGF single-nucleotide polymorphisms (SNPs) and social anhedonia has been confirmed (Ramos et al. 2014). In drug-naïve patients with first-onset paranoid schizophrenia, expression of amino acids 23-62 of the VGF protein was increased in cerebrospinal fluid (Huang et al. 2006, 2007). Moreover, the expression level of VGF was increased in fresh-frozen prefrontal cortex tissue (Brodmann area 9) of patients with schizophrenia by Western blot analysis (Huang et al. 2006). Only one study reported that the cell density of VGF-immunoactive neurons is reduced in hypothalamus of patients with schizophrenia, and the authors discussed that decreased intracellular content of VGF may reflect increased VGF protein secretion form hypothalamic neurons (Busse et al. 2012). In addition to the changes in expression, genetic association studies have been performed in patients with schizophrenia on chromosome 7q22 in which the human *VGF* gene is located. Previous two studies reported that an internal isolate in northeastern Finland, who have a higher lifetime prevalence of schizophrenia, have a schizophrenia susceptibility locus on chromosome 7q22 in sib-pair analyses (Hovatta et al. 1997; Ekelund et al. 2000; Wedenoja et al. 2008). Moreover, duplicated copy number variation (CNV) of 7q22.1 were found in patients with schizophrenia (Doherty et al. 2012; Rodriguez-Santiago et al. 2010; Walsh et al. 2008). Thus, these findings suggest that it is possible that downregulation or upregulation of VGF is involved in the pathophysiology of major depressive disorder and schizophrenia, although the evidence is only correlative and observational.

Basic Studies on the Influences of Downregulation of VGF in the CNS Using Transgenic Mice

To investigate the influences of downregulation of VGF, homozygous VGF knockout mice (VGF$^{-/-}$ mice) were generated (Hahm et al. 1999). VGF$^{-/-}$ mice are small infertile, and have a markedly reduced life span (Hahm et al. 1999). The first report on changes in the CNS of VGF knockout mice was published in 2007 (Hunsberger et al. 2007; Heldt et al. 2007). Heterozygous VGF knockout mice (VGF$^{+/-}$ mice) exhibit a higher depressive state in a forced swimming test and tail suspension test (Hunsberger et al. 2007; Heldt et al. 2007), indicating that VGF may be involved in the pathology of major depressive disorder. Moreover, many previous reports suggest that VGF-derived peptides, including TLQP-62 and AQEE-30 have antidepressant effects in mice (Hunsberger et al. 2007; Thakker-Varia et al. 2007; Lin et al. 2014; Li et al. 2017; Lv et al. 2018; Jiang et al. 2018a). In addition to the depressive state, contextual fear conditioning was impaired in VGF$^{-/-}$ mice and VGF$^{+/-}$ mice (Bozdagi et al. 2008). VGF$^{-/-}$ mice, but not VGF$^{+/-}$ mice, also showed memory deficits in the Morris water maze (Bozdagi et al. 2008). In an ex vivo study using hippocampal slices from VGF$^{-/-}$ mice and VGF$^{+/-}$ mice, long-term depression (LTD), which is implicated with the function of hippocampus, was impaired in VGF$^{-/-}$ mice, but not VGF$^{+/-}$ mice (Bozdagi et al. 2008; Brigman et al. 2010; Nicholls et al. 2008; Zamanillo et al. 1999; Zeng et al. 2001; Thakker-Varia et al. 2010). To investigate the role of VGF in the CNS more closely, brain-specific VGF knockout mice (αCamk2-Cre/+; *Vgf*$^{\text{flpflox/flpflox}}$ mice) were generated (Lin et al. 2015). Similar to VGF$^{+/-}$ mice, αCamk2-Cre/+; *Vgf*$^{\text{flpflox/flpflox}}$ mice have impaired long-term memory formation in contextual fear conditioning, but the impairment was not as well as VGF$^{-/-}$ mice do (Bozdagi et al. 2008; Lin et al. 2015). A recent study investigated the pathophysiology of and therapies for depression in brain-specific VGF knockout mice (Jiang et al. 2018b). Ketamine is a noncompetitive glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist. Ketamine had antidepressant effects in mice (Yang et al. 2015; Zanos et al. 2016). Moreover, ketamine had a rapid antidepressant effect that lasted for weeks in clinical trials (Zarate et al. 2006). In addition to the rapid antidepressant effect, ketamine is effective in treatment-resistant major depressive disorder patients (Murrough et al. 2013; Serafini et al. 2014; Limandri 2018). Therefore, ketamine attracts attention as a promising novel antidepressant. On this basis, Jiang et al. investigated the role of VGF in response to ketamine treatment. Ketamine had antidepressant effects in VGF$^{+/+}$ and AAV-GFP-injected *Vgf*$^{\text{flpflox/flpflox}}$ mouse littermates in the forced swimming test and a chronic social defeat stress model (Jiang et al. 2018b). Surprisingly, this antidepressant effect of ketamine was completely abolished in VGF$^{+/-}$ mice and intrahippocampal AAV-CreGFP-injected *Vgf*$^{\text{flpflox/flpflox}}$ mice (Jiang et al. 2018b). Phosphorylation of AMPA receptor (GluA) and mTOR signaling, both of which are implicated in the mediation of the antidepressant effect of ketamine, were increased in dorsal hippocampus dissected from AAV-GFP-injected *Vgf*$^{\text{flpflox/flpflox}}$ mouse littermates after administration of ketamine (Murrough et al. 2013; Li et al. 2010; Jiang et al. 2018b). However, increased phosphorylation of GluA and mTOR was not found in the dorsal hippocampus from AAV-CreGFP-injected *Vgf*$^{\text{flpflox/flpflox}}$ mice, revealing a possible molecular mechanism underlying these behaviors (Jiang et al. 2018b). Another study reported that ketamine rapidly reverses the chronic social defeat stress-induced depression behaviors, and knockdown of VGF on the prefrontal cortex cancels this effect in mice (Shen et al. 2018). Taken together, VGF may be involved in not only pathophysiology of depressive behavior but also the antidepressant mechanism of ketamine.

Basic Studies on the Influences of Upregulation of VGF in the CNS Using Transgenic Mice

To investigate the influences of upregulation of VGF, we generated VGF-overexpressing mice (Mizoguchi et al. 2017). Unlike VGF$^{-/-}$ mice, VGF-overexpressing mice are fertile (Mizoguchi et al. 2017). VGF-overexpressing mice exhibited several behavioral abnormalities, including hyperactivity, memory impairment, social deficits, and higher depressive states (Mizoguchi et al. 2017). In addition to abnormal behaviors, VGF-overexpressing mice exhibited morphological abnormalities, including smaller brain weight, expansion of the lateral ventricle, and striatal morphological abnormalities (Mizoguchi et al. 2017). Based on our first report, we investigated the influence of overexpression of VGF on the pathophysiology of schizophrenia. VGF-overexpressing mice exhibited sensorimotor gating deficits, which is an endophenotype of schizophrenia (Mizoguchi et al. 2018). In addition, the hyperactivity of VGF-overexpressing mice was suppressed by chronic administration of antipsychotics to same extents of antipsychotics treated wild-type mouse littermates (Mizoguchi et al. 2018). In addition to the changes during adult stage, the overexpression of VGF during developmental stage influenced the proper development of cerebellum (Mizoguchi et al. 2019). These finding suggest that the overexpression of VGF may be involved in the pathophysiology of schizophrenia. While we now have evidence that VGF affects behavior and morphological development of the brain, the molecular processes and the contribution of individual VGF-derived peptides to the pathology of schizophrenia remain unknown. Thus, it will be essential for future studies to address this in order to advance our current understanding of the molecular pathology of schizophrenia.

Discussion

In this review, we discussed the expression and genetic changes of VGF in patients with major depressive disorder and schizophrenia and the roles of VGF in the CNS, which have been revealed by transgenic animal models. Several previous studies using VGF knockout mice suggest that the downregulation of VGF may be related in the pathophysiology of major depressive disorder, and the effect of VGF

Table 1 The phenotypes of VGF knockout mice and VGF-overexpressing mice associated with depressive disorder and schizophrenia

Heterozygous VGF knockout mice	Higher depressive state	Hunsberger et al. (2007)
	Memory impairment	Bozdagi et al. (2008)
	Increased susceptibility to chronic social defeat stress	Jiang et al. (2018b)
	Abolished antidepressant effect for ketamine	
αCamk2-Cre/+, *Vgf*$^{\mathrm{flpflox/flpflox}}$ mice	Memory impairment	Lin et al. (2015)
Intrahippocampal AAV-CreGFP-injected *Vgf* flpflox/flpflox mice	Higher depressive state	Jiang et al. (2018b)
	Abolished antidepressant effect for ketamine	
VGF-overexpressing mice	Hyper locomotor activity, and normalized by administration with antipsychotics	Mizoguchi et al. (2017)
	Lower anxiety	Mizoguchi et al. (2018)
	Memory impairment	
	Higher depressive state	
	Lower sociability	
	Brain histological abnormalities	
	Prepulse inhibition impairment	

may regulate a novel antidepressant ketamine. Moreover, we revealed that VGF overexpression exhibited schizophrenia-like behaviors in mice, including sensorimotor gating deficits, which is an endophenotype of schizophrenia. Surprisingly, both hypomorphic and hypermorphic expression of VGF may produce several common behavioral phenotypes. It will be important to discover mechanisms that underlie the common behavioral abnormalities of VGF knockout and VGF-overexpressing mice. In previous reports, hypomorphic and hypermorphic expressions of BDNF have produced several common phenotypes (Papaleo et al. 2011; Heldt et al. 2007). The brain regions in which BDNF is ablated or overexpressed may be critical to the depressive phenotype. For instance, hippocampal BDNF ablation is prodepressant, while BDNF ablation in VTA projecting to NAc is antidepressant (Berton et al. 2006; Shirayama et al. 2002). A recent study revealed that VGF has opposite effects in the adult hippocampus and nucleus accumbens on depressive states by using region specific administration of AAV-CreGFP to *Vgf*$^{\mathrm{flpflox/flpflox}}$ mice and AAV-VGF (Jiang et al. 2018b). These results indicate that the brain region in which VGF is ablated or overexpressed may be critical to behavioral phenotypes. In addition to behavioral deficits, the studies using VGF knockout mice revealed that VGF is involved in glucose tolerance and hypertension (Stephens et al. 2017; Fargali et al. 2015). Clinically, there is evidence diabetes or hypertension in either major depressive disorder or schizophrenia (Badescu et al. 2016; Hoffman 2017; Licht et al. 2009; Morra and Strauss 2016). Thus, these reports suggest that the peripheral effects of VGF may be associated with the abnormal behaviors in VGF knockout mice and VGF-overexpressing mice (Table 1).

In addition to the expression changes of VGF in patients with major depressive disorder and schizophrenia, changes in VGF are reported at the experimental level in related major depressive disorder and schizophrenia. In terms of depression, VGF was decreased in hippocampus after both the learned helplessness and forced swim tests in mice (Thakker-Varia et al. 2007). In addition, treatments with fluoxetine and paroxetine increased the expression of VGF in astrocytes (Allaman et al. 2011). In terms of schizophrenia, the administration of phencyclidine (PCP), which is used in schizophrenia animal models, increased the expression of VGF in the prefrontal cortex, while VGF levels in the nucleus accumbens was decreased in rats (Kitaichi et al. 1994; Linn et al. 2003; Sams-Dodd 1995; Noli et al. 2017). In addition, chronic treatment with olanzapine decreased the expression level of VGF in the fronto-medial cortex in rats (Ersland et al. 2017). Both clinical and basic research outcomes suggest that VGF has disease-specific changes in the pathophysiology of major depressive disorder and schizophrenia and the administration of antidepressants or antipsychotics.

In conclusion, disturbance of the expression level of VGF may influence mental behaviors. It is useful for clarifying the differences between the pathophysiology of depression and schizophrenia to understand the roles of VGF in the CNS.

Author Contributions TM, MS, and HH wrote the paper. All authors reviewed the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Alder J, Thakker-Varia S, Bangasser DA, Kuroiwa M, Plummer MR, Shors TJ, Black IB (2003) Brain-derived neurotrophic factor-induced gene expression reveals novel actions of VGF in hippocampal synaptic plasticity. J Neurosci 23(34):10800–10808

Allaman I, Fiumelli H, Magistretti PJ, Martin JL (2011) Fluoxetine regulates the expression of neurotrophic/growth factors and glucose metabolism in astrocytes. Psychopharmacology 216(1):75–84. https://doi.org/10.1007/s00213-011-2190-y

Badescu SV, Tataru C, Kobylinska L, Georgescu EL, Zahiu DM, Zagrean AM, Zagrean L (2016) The association between diabetes mellitus and depression. J Med Life 9(2):120–125

Benson DL, Salton SR (1996) Expression and polarization of VGF in developing hippocampal neurons. Brain Res Dev Brain Res 96(1–2):219–228

Berton O, McClung CA, Dileone RJ, Krishnan V, Renthal W, Russo SJ, Graham D, Tsankova NM, Bolanos CA, Rios M, Monteggia LM, Self DW, Nestler EJ (2006) Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. Science 311(5762):864–868. https://doi.org/10.1126/science.1120972

Bonni A, Ginty DD, Dudek H, Greenberg ME (1995) Serine 133-phosphorylated CREB induces transcription via a cooperative mechanism that may confer specificity to neurotrophin signals. Mol Cell Neurosci 6(2):168–183. https://doi.org/10.1006/mcne.1995.1015

Bozdagi O, Rich E, Tronel S, Sadahiro M, Patterson K, Shapiro ML, Alberini CM, Huntley GW, Salton SR (2008) The neurotrophin-inducible gene Vgf regulates hippocampal function and behavior through a brain-derived neurotrophic factor-dependent mechanism. J Neurosci 28(39):9857–9869. https://doi.org/10.1523/JNEUROSCI.3145-08.2008

Brigman JL, Wright T, Talani G, Prasad-Mulcare S, Jinde S, Seabold GK, Mathur P, Davis MI, Bock R, Gustin RM, Colbran RJ, Alvarez VA, Nakazawa K, Delpire E, Lovinger DM, Holmes A (2010) Loss of GluN2B-containing NMDA receptors in CA1 hippocampus and cortex impairs long-term depression, reduces dendritic spine density, and disrupts learning. J Neurosci 30(13):4590–4600. https://doi.org/10.1523/JNEUROSCI.0640-10.2010

Busse S, Bernstein HG, Busse M, Bielau H, Brisch R, Mawrin C, Muller S, Sarnyai Z, Gos T, Bogerts B, Steiner J (2012) Reduced density of hypothalamic VGF-immunoreactive neurons in schizophrenia: a potential link to impaired growth factor signaling and energy homeostasis. Eur Arch Psychiatry Clin Neurosci 262(5):365–374. https://doi.org/10.1007/s00406-011-0282-7

Cattaneo A, Bocchio-Chiavetto L, Zanardini R, Milanesi E, Placentino A, Gennarelli M (2010a) Reduced peripheral brain-derived neurotrophic factor mRNA levels are normalized by antidepressant treatment. Int J Neuropsychopharmacol 13(1):103–108. https://doi.org/10.1017/s1461145709990812

Cattaneo A, Sesta A, Calabrese F, Nielsen G, Riva MA, Gennarelli M (2010b) The expression of VGF is reduced in leukocytes of depressed patients and it is restored by effective antidepressant treatment. Neuropsychopharmacology 35(7):1423–1428. https://doi.org/10.1038/npp.2010.11

Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, Craig IW, Anacker C, Zunsztain PA, McGuffin P, Pariante CM (2013) Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology 38(3):377–385. https://doi.org/10.1038/npp.2012.191

Chen S, Jiang H, Hou Z, Yue Y, Zhang Y, Zhao F, Xu Z, Li Y, Mou X, Li L, Wang T, Zhao J, Han C, Sui Y, Wang M, Yang Z, Lu Y, Zhu Y, Li J, Shen X, Sun F, Chen Q, Yuan Y (2018) Higher serum VGF protein levels discriminate bipolar depression from major depressive disorder. J Neurosci Res. https://doi.org/10.1002/jnr.24377

Doherty JL, O'Donovan MC, Owen MJ (2012) Recent genomic advances in schizophrenia. Clin Genet 81(2):103–109. https://doi.org/10.1111/j.1399-0004.2011.01773.x

Ekelund J, Lichtermann D, Hovatta I, Ellonen P, Suvisaari J, Terwilliger JD, Juvonen H, Varilo T, Arajarvi R, Kokko-Sahin ML, Lonnqvist J, Peltonen L (2000) Genome-wide scan for schizophrenia in the Finnish population: evidence for a locus on chromosome 7q22. Hum Mol Genet 9(7):1049–1057

Ellis KL, Zhou Y, Rodriguez-Murillo L, Beshansky JR, Ainehsazan E, Selker HP, Huggins GS, Cupples LA, Peter I (2017) Common variants associated with changes in levels of circulating free fatty acids after administration of glucose-insulin-potassium (GIK) therapy in the IMMEDIATE trial. Pharmacogenomics J 17(1):76–83. https://doi.org/10.1038/tpj.2015.84

Ersland KM, Skrede S, Stansberg C, Steen VM (2017) Subchronic olanzapine exposure leads to increased expression of myelination-related genes in rat fronto-medial cortex. Transl Psychiatry 7(11):1262. https://doi.org/10.1038/s41398-017-0008-3

Fargali S, Garcia AL, Sadahiro M, Jiang C, Janssen WG, Lin WJ, Cogliani V, Elste A, Mortillo S, Cero C, Veitenheimer B, Graiani G, Pasinetti GM, Mahata SK, Osborn JW, Huntley GW, Phillips GR, Benson DL, Bartolomucci A, Salton SR (2015) Erratum. The granin VGF promotes genesis of secretory vesicles, and regulates circulating catecholamine levels and blood pressure. FASEB J 29(6):2679. https://doi.org/10.1096/fj.13-239509err

Ferri GL, Levi A, Possenti R (1992) A novel neuroendocrine gene product: selective VGF8a gene expression and immuno-localisation of the VGF protein in endocrine and neuronal populations. Brain Res Mol Brain Res 13(1–2):139–143

Ferri GL, Noli B, Brancia C, D'Amato F, Cocco C (2011) VGF: an inducible gene product, precursor of a diverse array of neuroendocrine peptides and tissue-specific disease biomarkers. J Chem Neuroanat 42(4):249–261. https://doi.org/10.1016/j.jchemneu.2011.05.007

Hahm S, Mizuno TM, Wu TJ, Wisor JP, Priest CA, Kozak CA, Boozer CN, Peng B, McEvoy RC, Good P, Kelley KA, Takahashi JS, Pintar JE, Roberts JL, Mobbs CV, Salton SR (1999) Targeted deletion of the Vgf gene indicates that the encoded secretory peptide precursor plays a novel role in the regulation of energy balance. Neuron 23(3):537–548

Heldt SA, Stanek L, Chhatwal JP, Ressler KJ (2007) Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol Psychiatry 12(7):656–670. https://doi.org/10.1038/sj.mp.4001957

Hoffman RP (2017) The complex inter-relationship between diabetes and schizophrenia. Curr Diabetes Rev 13(3):528–532. https://doi.org/10.2174/1573399812666161201205322

Hovatta I, Terwilliger JD, Lichtermann D, Makikyro T, Suvisaari J, Peltonen L, Lonnqvist J (1997) Schizophrenia in the genetic isolate of Finland. Am J Med Genet 74(4):353–360

Huang JT, Leweke FM, Oxley D, Wang L, Harris N, Koethe D, Gerth CW, Nolden BM, Gross S, Schreiber D, Reed B, Bahn S (2006) Disease biomarkers in cerebrospinal fluid of patients with first-onset psychosis. PLoS Med 3(11):e428. https://doi.org/10.1371/journal.pmed.0030428

Huang JT, Leweke FM, Tsang TM, Koethe D, Kranaster L, Gerth CW, Gross S, Schreiber D, Ruhrmann S, Schultze-Lutter F, Klosterkotter J, Holmes E, Bahn S (2007) CSF metabolic and proteomic profiles in patients prodromal for psychosis. PLoS ONE 2(8):e756. https://doi.org/10.1371/journal.pone.0000756

Hunsberger JG, Newton SS, Bennett AH, Duman CH, Russell DS, Salton SR, Duman RS (2007) Antidepressant actions of the exercise-regulated gene VGF. Nat Med 13(12):1476–1482. https://doi.org/10.1038/nm1669

Jiang H, Chen S, Lu N, Yue Y, Yin Y, Zhang Y, Jiang W, Liang J, Yuan Y (2017) Reduced serum VGF levels were reversed by antidepressant treatment in depressed patients. World J Biol Psychiatry 18(8):586–591. https://doi.org/10.1080/15622975.2016.1224923

Jiang C, Lin WJ, Labonte B, Tamminga CA, Turecki G, Nestler EJ, Russo SJ, Salton SR (2018a) VGF and its C-terminal peptide TLQP-62 in ventromedial prefrontal cortex regulate depression-related behaviors and the response to ketamine. Neuropsychopharmacology. https://doi.org/10.1038/s41386-018-0277-4

Jiang C, Lin WJ, Sadahiro M, Labonte B, Menard C, Pfau ML, Tamminga CA, Turecki G, Nestler EJ, Russo SJ, Salton SR (2018b) VGF function in depression and antidepressant efficacy. Mol Psychiatry 23(7):1632–1642. https://doi.org/10.1038/mp.2017.233

Jiang C, Lin WJ, Salton SR (2018c) Role of a VGF/BDNF/TrkB autoregulatory feedback loop in rapid-acting antidepressant efficacy. J Mol Neurosci. https://doi.org/10.1007/s12031-018-1124-0

Kitaichi K, Yamada K, Hasegawa T, Furukawa H, Nabeshima T (1994) Effects of risperidone on phencyclidine-induced behaviors: comparison with haloperidol and ritanserin. Jpn J Pharmacol 66(2):181–189

Laslop A, Mahata SK, Wolkersdorfer M, Mahata M, Srivastava M, Seidah NG, Fischer-Colbrie R, Winkler H (1994) Large dense-core vesicles in rat adrenal after reserpine: levels of mRNAs of soluble and membrane-bound constituents in chromaffin and ganglion cells indicate a biosynthesis of vesicles with higher secretory quanta. J Neurochem 62(6):2448–2456

Levi A, Eldridge JD, Paterson BM (1985) Molecular cloning of a gene sequence regulated by nerve growth factor. Science 229(4711):393–395

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329(5994):959–964. https://doi.org/10.1126/science.1190287

Li C, Li M, Yu H, Shen X, Wang J, Sun X, Wang Q, Wang C (2017) Neuropeptide VGF C-terminal peptide TLQP-62 alleviates lipopolysaccharide-induced memory deficits and anxiety-like and depression-like behaviors in mice: the role of BDNF/TrkB signaling. ACS Chem Neurosci 8(9):2005–2018. https://doi.org/10.1021/acschemneuro.7b00154

Licht CM, de Geus EJ, Seldenrijk A, van Hout HP, Zitman FG, van Dyck R, Penninx BW (2009) Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension 53(4):631–638. https://doi.org/10.1161/hypertensionaha.108.126698

Limandri BJ (2018) Ketamine for treatment-resistant depression: a gateway to novel treatment approaches. J Psychosoc Nurs Ment Health Serv 56(10):11–14. https://doi.org/10.3928/02793695-20180920-02

Lin P, Wang C, Xu B, Gao S, Guo J, Zhao X, Huang H, Zhang J, Chen X, Wang Q, Zhou W (2014) The VGF-derived peptide TLQP62 produces antidepressant-like effects in mice via the BDNF/TrkB/CREB signaling pathway. Pharmacol Biochem Behav 120:140–148. https://doi.org/10.1016/j.pbb.2014.03.003

Lin WJ, Jiang C, Sadahiro M, Bozdagi O, Vulchanova L, Alberini CM, Salton SR (2015) VGF and its C-terminal peptide TLQP-62 regulate memory formation in hippocampus via a BDNF-TrkB-dependent mechanism. J Neurosci 35(28):10343–10356. https://doi.org/10.1523/JNEUROSCI.0584-15.2015

Linn GS, Negi SS, Gerum SV, Javitt DC (2003) Reversal of phencyclidine-induced prepulse inhibition deficits by clozapine in monkeys. Psychopharmacology 169(3–4):234–239. https://doi.org/10.1007/s00213-003-1533-8

Lv D, Chen Y, Shen M, Liu X, Zhang Y, Xu J, Wang C (2018) Mechanisms underlying the rapid-acting antidepressant-like effects of neuropeptide VGF (non-acronymic) C-terminal peptide TLQP-62. Neuropharmacology 143:317–326. https://doi.org/10.1016/j.neuropharm.2018.09.046

Mizoguchi T, Minakuchi H, Ishisaka M, Tsuruma K, Shimazawa M, Hara H (2017) Behavioral abnormalities with disruption of brain structure in mice overexpressing VGF. Sci Rep 7(1):4691. https://doi.org/10.1038/s41598-017-04132-7

Mizoguchi T, Minakuchi H, Tanaka M, Tsuruma K, Shimazawa M, Hara H (2018) Sensorimotor gating deficits and effects of antipsychotics on the hyperactivity in VGF-overexpressing mice. Pharmacol Rep 70(3):476–480. https://doi.org/10.1016/j.pharep.2017.11.013

Mizoguchi T, Shimazawa M, Ohuchi K, Kuse Y, Nakamura S, Hara H (2019) Impaired cerebellar development in mice overexpressing VGF. Neurochem Res 44(2):374–387. https://doi.org/10.1007/s11064-018-2684-7

Morra LF, Strauss GP (2016) Severity of hypertension predicts the generalized neurocognitive deficit in schizophrenia. Schizophr Res 176(2–3):527–528. https://doi.org/10.1016/j.schres.2016.07.001

Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, Collins KA, Mathew SJ, Charney DS, Iosifescu DV (2013) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 74(4):250–256. https://doi.org/10.1016/j.biopsych.2012.06.022

Nicholls RE, Alarcon JM, Malleret G, Carroll RC, Grody M, Vronskaya S, Kandel ER (2008) Transgenic mice lacking NMDAR-dependent LTD exhibit deficits in behavioral flexibility. Neuron 58(1):104–117. https://doi.org/10.1016/j.neuron.2008.01.039

Noda Y, Shimazawa M, Tanaka H, Tamura S, Inoue T, Tsuruma K, Hara H (2015) VGF and striatal cell damage in in vitro and in vivo models of Huntington's disease. Pharmacol Res Perspect 3(3):e00140. https://doi.org/10.1002/prp2.140

Noda Y, Motoyama S, Nakamura S, Shimazawa M, Hara H (2019) Neuropeptide VGF-derived peptide LQEQ-19 has neuroprotective effects in an in vitro model of amyotrophic lateral sclerosis. Neurochem Res. https://doi.org/10.1007/s11064-019-02725-4

Noli B, Sanna F, Brancia C, D'Amato F, Manconi B, Vincenzoni F, Messana I, Melis MR, Argiolas A, Ferri GL, Cocco C (2017) Profiles of VGF peptides in the rat brain and their modulations after phencyclidine treatment. Front Cell Neurosci 11:158. https://doi.org/10.3389/fncel.2017.00158

Papaleo F, Silverman JL, Aney J, Tian Q, Barkan CL, Chadman KK, Crawley JN (2011) Working memory deficits, increased anxiety-like traits, and seizure susceptibility in BDNF overexpressing mice. Learn Mem 18(8):534–544. https://doi.org/10.1101/lm.2213711

Petrocchi-Passeri P, Cero C, Cutarelli A, Frank C, Severini C, Bartolomucci A, Possenti R (2015) The VGF-derived peptide TLQP-62 modulates insulin secretion and glucose homeostasis. J Mol Endocrinol 54(3):227–239. https://doi.org/10.1530/jme-14-0313

Possenti R, Eldridge JD, Paterson BM, Grasso A, Levi A (1989) A protein induced by NGF in PC12 cells is stored in secretory vesicles and released through the regulated pathway. EMBO J 8(8):2217–2223

Ramos A, Rodriguez-Seoane C, Rosa I, Trossbach SV, Ortega-Alonso A, Tomppo L, Ekelund J, Veijola J, Jarvelin MR, Alonso J, Veiga S, Sawa A, Hennah W, Garcia A, Korth C, Requena JR (2014) Neuropeptide precursor VGF is genetically associated with social anhedonia and underrepresented in the brain of major mental illness: its downregulation by DISC1. Hum Mol Genet 23(22):5859–5865. https://doi.org/10.1093/hmg/ddu303

Rodriguez-Santiago B, Brunet A, Sobrino B, Serra-Juhe C, Flores R, Armengol L, Vilella E, Gabau E, Guitart M, Guillamat R, Martorell L, Valero J, Gutierrez-Zotes A, Labad A, Carracedo

A, Estivill X, Perez-Jurado LA (2010) Association of common copy number variants at the glutathione S-transferase genes and rare novel genomic changes with schizophrenia. Mol Psychiatry 15(10):1023–1033. https://doi.org/10.1038/mp.2009.53

Salton SR, Fischberg DJ, Dong KW (1991) Structure of the gene encoding VGF, a nervous system-specific mRNA that is rapidly and selectively induced by nerve growth factor in PC12 cells. Mol Cell Biol 11(5):2335–2349

Sams-Dodd F (1995) Automation of the social interaction test by a video-tracking system: behavioural effects of repeated phencyclidine treatment. J Neurosci Methods 59(2):157–167

Serafini G, Howland RH, Rovedi F, Girardi P, Amore M (2014) The role of ketamine in treatment-resistant depression: a systematic review. Curr Neuropharmacol 12(5):444–461. https://doi.org/10.2174/1570159X12666140619204251

Severini C, Ciotti MT, Biondini L, Quaresima S, Rinaldi AM, Levi A, Frank C, Possenti R (2008) TLQP-21, a neuroendocrine VGF-derived peptide, prevents cerebellar granule cells death induced by serum and potassium deprivation. J Neurochem 104(2):534–544. https://doi.org/10.1111/j.1471-4159.2007.05068.x

Shen M, Lv D, Liu X, Li S, Chen Y, Zhang Y, Wang Z, Wang C (2018) Essential roles of neuropeptide VGF regulated TrkB/mTOR/BICC1 signaling and phosphorylation of AMPA receptor subunit GluA1 in the rapid antidepressant-like actions of ketamine in mice. Brain Res Bull 143:58–65. https://doi.org/10.1016/j.brainresbull.2018.10.004

Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS (2002) Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 22(8):3251–3261

Snyder SE, Salton SR (1998) Expression of VGF mRNA in the adult rat central nervous system. J Comp Neurol 394(1):91–105

Snyder SE, Cheng HW, Murray KD, Isackson PJ, McNeill TH, Salton SR (1998) The messenger RNA encoding VGF, a neuronal peptide precursor, is rapidly regulated in the rat central nervous system by neuronal activity, seizure and lesion. Neuroscience 82(1):7–19

Stephens SB, Schisler JC, Hohmeier HE, An J, Sun AY, Pitt GS, Newgard CB (2012) A VGF-derived peptide attenuates development of type 2 diabetes via enhancement of islet beta-cell survival and function. Cell Metab 16(1):33–43. https://doi.org/10.1016/j.cmet.2012.05.011

Stephens SB, Edwards RJ, Sadahiro M, Lin WJ, Jiang C, Salton SR, Newgard CB (2017) The prohormone VGF regulates beta cell function via insulin secretory granule biogenesis. Cell Rep 20(10):2480–2489. https://doi.org/10.1016/j.celrep.2017.08.050

Takeuchi H, Inagaki S, Morozumi W, Nakano Y, Inoue Y, Kuse Y, Mizoguchi T, Nakamura S, Funato M, Kaneko H, Hara H, Shimazawa M (2018) VGF nerve growth factor inducible is involved in retinal ganglion cells death induced by optic nerve crush. Sci Rep 8(1):16443. https://doi.org/10.1038/s41598-018-34585-3

Thakker-Varia S, Krol JJ, Nettleton J, Bilimoria PM, Bangasser DA, Shors TJ, Black IB, Alder J (2007) The neuropeptide VGF produces antidepressant-like behavioral effects and enhances proliferation in the hippocampus. J Neurosci 27(45):12156–12167. https://doi.org/10.1523/JNEUROSCI.1898-07.2007

Thakker-Varia S, Jean YY, Parikh P, Sizer CF, Jernstedt Ayer J, Parikh A, Hyde TM, Buyske S, Alder J (2010) The neuropeptide VGF is reduced in human bipolar postmortem brain and contributes to some of the behavioral and molecular effects of lithium. J Neurosci 30(28):9368–9380. https://doi.org/10.1523/JNEUROSCI.5987-09.2010

van den Pol AN, Bina K, Decavel C, Ghosh P (1994) VGF expression in the brain. J Comp Neurol 347(3):455–469. https://doi.org/10.1002/cne.903470311

Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, Kusenda M, Malhotra D, Bhandari A, Stray SM, Rippey CF, Roccanova P, Makarov V, Lakshmi B, Findling RL, Sikich L, Stromberg T, Merriman B, Gogtay N, Butler P, Eckstrand K, Noory L, Gochman P, Long R, Chen Z, Davis S, Baker C, Eichler EE, Meltzer PS, Nelson SF, Singleton AB, Lee MK, Rapoport JL, King MC, Sebat J (2008) Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320(5875):539–543. https://doi.org/10.1126/science.1155174

Wedenoja J, Loukola A, Tuulio-Henriksson A, Paunio T, Ekelund J, Silander K, Varilo T, Heikkila K, Suvisaari J, Partonen T, Lonnqvist J, Peltonen L (2008) Replication of linkage on chromosome 7q22 and association of the regional Reelin gene with working memory in schizophrenia families. Mol Psychiatry 13(7):673–684. https://doi.org/10.1038/sj.mp.4002047

Yamaguchi H, Sasaki K, Satomi Y, Shimbara T, Kageyama H, Mondal MS, Toshinai K, Date Y, Gonzalez LJ, Shioda S, Takao T, Nakazato M, Minamino N (2007) Peptidomic identification and biological validation of neuroendocrine regulatory peptide-1 and -2. J Biol Chem 282(36):26354–26360. https://doi.org/10.1074/jbc.M701665200

Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, Dong C, Hashimoto K (2015) R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl Psychiatry 5:e632. https://doi.org/10.1038/tp.2015.136

Zamanillo D, Sprengel R, Hvalby O, Jensen V, Burnashev N, Rozov A, Kaiser KM, Koster HJ, Borchardt T, Worley P, Lubke J, Frotscher M, Kelly PH, Sommer B, Andersen P, Seeburg PH, Sakmann B (1999) Importance of AMPA receptors for hippocampal synaptic plasticity but not for spatial learning. Science 284(5421):1805–1811

Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, Elmer GI, Alkondon M, Yuan P, Pribut HJ, Singh NS, Dossou KS, Fang Y, Huang XP, Mayo CL, Wainer IW, Albuquerque EX, Thompson SM, Thomas CJ, Zarate CA Jr, Gould TD (2016) NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533(7604):481–486. https://doi.org/10.1038/nature17998

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63(8):856–864. https://doi.org/10.1001/archpsyc.63.8.856

Zeng H, Chattarji S, Barbarosie M, Rondi-Reig L, Philpot BD, Miyakawa T, Bear MF, Tonegawa S (2001) Forebrain-specific calcineurin knockout selectively impairs bidirectional synaptic plasticity and working/episodic-like memory. Cell 107(5):617–629

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.