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Grape-derived polyphenols produce antidepressant effects via VGF- and BDNF-dependent mechanisms

Cheng Jiang[1], **Emmy Sakakibara**[1], **Wei-Jye Lin**[1,5,6], **Jun Wang**[3], **Giulio M. Pasinetti**[3], **Stephen R. Salton**[*,1,2,4]

[1]Department of Neuroscience, Icahn School of Sinai, New York, NY 10029, USA

[2]Department of Geriatrics, Icahn School of Sinai, New York, NY 10029, USA

[3]Department of Neurology, Icahn School of Sinai, New York, NY 10029, USA

[4]Friedman Brain Institute, Icahn School of Sinai, New York, NY 10029, USA

[5]RNA Biomedical Institute, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, Guangdong, 510120, China

[6]Guangdong Province Key Laboratory of Brain Function and Disease, Zhongshan Schoofof Medicine, Sun Yat-sen University, 74 Zhongshan 2nd Road, Guangzhou,Guangdong, China

Abstract

Recent studies suggest that Bioactive Dietary Polyphenol Preparation (BDPP) and individual polyphenolic compounds ameliorate stress-induced depression-like behaviors, but the underlying molecular mechanisms are incompletely understood. VGF (non-acronymic) in dorsal hippocampus (dHc) has been shown to play a role in depression-like behavior and antidepressant efficacy, and the VGF-derived peptide TLQP-62 (named by the N-terminal 4 amino acids and length) infused into dHc has been shown to have antidepressant efficacy that is BDNF/TrkB dependent. Here, we investigated whether BDPP influences VGF expression in dHc, and whether dHc VGF is required for BDPP antidepressant efficacy. We found that BDPP produced antidepressant-like effects in naive mice and reversed the depression-like behaviors induced by chronic variable stress (CVS). In addition, we found that BDPP had no detectable antidepressant efficacy in floxed mice with prior knockdown in dHc of either VGF or BDNF, achieved by adeno- associated virus (AAV)-Cre infusion. Our data indicate that dHc VGF and BDNF expression are required for the antidepressant actions of BDPP, and therefore suggest that a VGF(TLQP-62)/BDNF/TrkB autoregulatory feedback loop could play a role in the regulation of BDPP antidepressant efficacy, much as it has been suggested to function in the antidepressant efficacies of ketamine and TLQP-62.

[*]Corresponding author: Dr. Stephen R. Salton, Department of Neuroscience, Box 1639, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York NY, 10029 USA Tel: 1-212-824-9308; Fax: 1-646-537-9583; stephen.salton@mssm.edu.

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COMPETING INTERESTS

The authors have no competing interests to disclose.

Keywords

Antidepressant; Brain-Derived Neurotophic Factor (BDNF); Chronic Variable Stress (CVS); Grape Seed Polyphenolic Extract (GSPE); Major Depressive Disorder (MDD); Polyphenol

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental illness [1] with limited effective treatment options available. The delayed onset of action [2] and unpleasant side effects [3] of conventional antidepressant drugs make development of safer, more effective and tolerable treatments an urgent need.

Polyphenols are a group of chemical compounds with antioxidant property that naturally exist in our diet [4,5]. Polyphenols has been shown to contribute to the prevention of cardiovascular diseases, cancers, diabetes and osteoporosis [6]. Among them are grape-derived polyphenols, which have been shown to promote cognitive functions in preclinical Alzheimer's disease (AD) models [7,8] potentially by improving synaptic plasticity[9]. In addition, grape-derived polyphenols such as proanthocyanidin and resveratrol produce antidepressant effects in animal models of depression [10,11]. Recently, a novel polyphenol preparation - Bioactive Dietary Polyphenol Preparation (BDPP) - which consists of grape seed polyphenol extract (GSPE), resveratrol and Concord grape juice (CGJ) has been reported to prevent cognitive deficits induced by sleep deprivation [12], protect against amyloid accumulation in a mouse AD model [13], and reverse social avoidance behaviors induced by chronic social defeat stress [14]

VGF (non-acronymic) is a neuropeptide precursor that is robustly regulated by neurotrophic factors [15,16]. VGF expression is reduced in human postmortem hippocampus and prefrontal cortex while it is increased in nucleus accumbens by MDD [17,18]. VGF has antidepressant efficacy in hippocampus and prefrontal cortex while it is pro-depressant in nucleus accumbens [17,18]. Treatment with antidepressants, such as ketamine and imipramine, or exercise increases VGF expression in hippocampus and prefrontal cortex [17–20]. Moreover, VGF expression in hippocampus and prefrontal cortex is required for the actions of antidepressant agents [17,18]. VGF and its C-terminal peptides regulate depression [17–20] and memory formation [21, 22] potentially by influencing synaptic plasticity and neurogenesis [16-23]. In addition, published evidence suggests that α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluR1 is associated with depression-like behaviors [24] and response to stress [25] as well as antidepressant treatments [26,27]. In the present study, we investigated whether VGF is associated with the antidepressant actions of BDPP and explored its potential underlying molecular mechanisms.

MATERIALS AND METHODS

Animals

Generation of loxp-flanked (floxed) VGF mice and breeding to remove the FRT-flanked neomycin selection cassette, generating $Vgf^{flpflox/flpflox}$ mice (abbreviated here $Vgf^{ff/ff}$), has been previously described [22]. Male C57BL/6J, $Vgf^{ff/ff}$ BDNF floxed [28] (designated

Bdnf$^{flox/flox}$ BL6/sv129 background; generously provided by Dr. Eric Nestler) at 2 – 3 months of age were housed on a 12 h light-dark cycle with ad libitum access to food and water. All mice were single housed at least 3 days prior to the start of behavioral experiments. All mouse studies were conducted in accordance with the U.S. National Institutes of Health Guidelines for the Care and Use of Experimental Animals, using protocols approved by the Institutional Animal Care and Use Committee of the Icahn School of Medicine at Mount Sinai.

General experimental methods

Experimental sample sizes were estimated on the basis of published studies and/or power analysis. Values were excluded from completed experiments and analyses only if they were detected as outliers by Grubb's test. This criterion was pre-established. Mice of the same gender were randomly assigned to different experimental groups with age and weight matched as closely as possible.

Special diets and BDPP treatment

AIN-93M purified rodent diet (D10012M) was obtained from Research Diets, Inc. (New Brunswick, NJ, USA). Resveratrol (ChromaDex, Irvine, CA, USA), GSPE (Warehouse, UPC: 603573579173), CGJ (Welch) were dissolved or diluted in water. The calculated daily intake of GSPE was 200 mg/kg body weight (BW), Resveratrol was 200 mg/kg BW and CGJ was 1 ml/day. All mice were acclimated for a week on the AIN-93M diet before BDPP treatment.

Stereotaxic viral infusion

Vgf$^{ff/ff}$ or *BDNF*$^{flox/flox}$ mice at 2 – 3 months of age were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg). Thirty-three gauge syringe needles (Hamilton, Reno, Nevada) were used to bilaterally infuse 1.0 μl of AAV virus into mouse dorsal hippocampus (dHc) (AP = −2.0, ML = ±1.5, and DV = −2.0 from Bregma (mm)) at a rate of 0.2 μl per min, and the needle was allowed to remain in place for 5 min before removal to prevent backflow. AAV-CreGFP and AAV-GFP (AAV2 genotype, AAV5 serotype) were prepared by the Vector Core at the University of North Carolina at Chapel Hill. AAV-injected mice were allowed to recover for 21 days before treatment.

Chronic variable stress

Chronic variable stress (CVS) was performed as described previously. Briefly, it consisted of three different stressors (foot shock, tail suspension and restraint stress) that were alternated over 21 days to avoid habituation. On day 1, foot shock consisted of 100 random mild electric shocks at 0.45 mA over 1 hour. On day 2, tail suspension stress lasted 1 hour. On day 3, restraint stress was applied by placing mice into 50 ml conical tubes for 1 hour within their home cages. The same stressors were repeated for the next 18 days in the same order.

Forced swim test

Forced swim test (FST) was performed under bright light. Mice were placed in 4L beakers containing ~ 3L of tap water at a temperature of 25 ± 1 °C for 6 min. Behavior was recorded

and immobility time, defined as the absence of any movement except that necessary for the mice to keep their heads above water, was manually counted over the last 4 minutes.

Open field test

The open field test (OFT) was performed under red light. Mice were placed in an open field arena (44 × 44 cm), and video tracking software (Ethovision 3.0, Noldus Information Technology, Leesburg, Virginia) was used to measure total movement of mice over 10 minutes.

Sucrose splash test

The sucrose splash test (SST) was performed as described previously [29]. Briefly, mice were sprayed with 10% sucrose solution onto their dorsal coat in their home cages under red light. After the sucrose solution was applied, behavior was recorded for 5 minutes. The time spent grooming was manually counted for the entire 5 minutes.

Protein sample preparation and western blotting

To prepare total homogenate, mouse dorsal hippocampus (dHc) was homogenized in ice-cold protein lysis buffer containing 50 mM Tris-HCl (pH 7.5), 140 mM NaCl, 1% TritonX100, 0.5% Na Deoxycholate, 0.1% SDS and 2mM EDTA with 1x Halt Protease and Phosphatase Inhibitor Cocktail (Thermo Fisher Scientific, Waltham, Massachusetts). To quantify total GluR1 level, crude synaptosomes were prepared by minor modification of an established protocol[30]. Briefly, dissected dHc was homogenized in ice-cold solution containing 320 mM sucrose, 20 mM HEPES (pH 7.4), 1 mM EDTA with 1x Halt Protease and Phosphatase Inhibitor Cocktail. The homogenate was centrifuged at 1000 ×g for 10 min at 4°C, generating a pellet (nuclear fraction) and supernatant. The supernatant was then centrifuged at 10,000 ×g for 10 min at 4°C, the supernatant (cytosolic fraction) was removed, and the pellet (crude synaptosomal fraction) was resuspended in protein lysis buffer described above. Protein concentration was determined by Bio-Rad protein assay (Bio-Rad Laboratories, Hercules, California), and equal protein amounts (10 μg per lane) were resolved on denaturing 10% SDS-PAGE gels and transferred by electroblotting to Hybond-P PVDF membranes (Millipore, Billerica, Massachusetts). Membranes were blocked in 10% non-fat milk/PBS for 1 h at room temperature, and then were incubated with either anti-VGF C-terminal (1:2000, rabbit polyclonal), anti-β-actin (1:3000, # MAB1501, Millipore, Billerica, Massachusetts), or anti-total-GluR1 (1:1000, # 13185, Cell Signaling Technology, Danvers, Massachusetts) in 3% BSA in PBS at 4°C overnight. Membranes were washed in PBST (0.2% Tween-20 in PBS), incubated with a secondary horseradish peroxidase- labelled donkey anti-rabbit or donkey anti-mouse antibody (1:6000, #NA934 and # NA931, GE Healthcare, Piscataway, New Jersey) for 1 h, washed again in PBST and incubated with ECL detection reagents (Millipore, Billerica, Massachusetts). Densitometric analysis was performed using NIH ImageJ software, and protein levels were normalized to β-actin.

Statistical analysis.

Statistical analyses were performed using GraphPad Prism 7. Comparisons for four groups were made using two-way analysis of variance (ANOVA) followed by Fisher's Least Significant Difference (LSD) test as indicated in the Figure Legends. All tests are two-sided. All data are presented as mean ± s.e.m.

RESULTS

BDPP treatment produces antidepressant effects in naive mice and prevents the development of depression-like behaviors following chronic variable stress

To determine the antidepressant effects of BDPP administration, we treated male wild- type mice with BDPP or water (vehicle) throughout the 21-day chronic variable stress (CVS) protocol and behaviorally assessed them subsequently (Figure 1A). Another cohort of mice was subjected to the same BDPP treatment without exposure to CVS to serve as a naive control. BDPP treatment did not affect locomotor activity in both naive mice and CVS-exposed mice (Figure 1B). BDPP-treated naive mice showed increased grooming time in the SST (Figure 1C) and decreased immobility time in the FST (Figure 1D) compared to control mice. CVS exposure reduced grooming time in the SST and increased immobility time in the FST in water-treated, but not BDPP-treated mice (Figure 1C, D).

BDPP treatment up-regulates VGF expression in dorsal hippocampus

To investigate whether VGF is regulated in the dHc by BDPP, dHc from an independent cohort of naive mice (without behavioral assessment) was dissected after 17 days of BDPP treatment for western blot analysis (Figure 2A). VGF protein levels were significantly increased in dHc total homogenate of BDPP-treated mice compared to water-treated controls (Figure 2B).

Dorsal hippocampal VGF expression is required for the antidepressant efficacy of BDPP treatment

To determine whether VGF expression in dHc is required for the antidepressant effects of BDPP, we treated AAV-Cre or AAV-GFP-injected loxp-flanked (floxed) VGF mice (with the FRT-flanked neomycin selection cassette removed, these homozygous mice are designated $Vgf^{f/f}$) with BDPP or water for 17 days, and then we subsequently assessed their behavioral phenotypes (Figure 3A). BDPP did not affect locomotor activity (Figure 3B), but induced antidepressant effects in dHc AAV-GFP-injected $Vgf^{f/f}$ mice in the SST (Figure 3C) and FST (Figure 3D). However, these effects were completely absent in dHc AAV-Cre-injected $Vgf^{f/f}$ mice, suggesting that dHc VGF is required for the antidepressant actions of BDPP. As we have seen in past studies [17], AAV-Cre-mediated ablation of VGF in dHc alone did not significantly affect immobility time in the FST following other behavioral tests or experimental procedures (i.e. in AAV-Cre-injected $Vgf^{f/f}$ mice treated with water in Fig. 3, or injected with saline in previous experiments [17]).

BDPP treatment up-regulates GluR1 levels in dorsal hippocampal synaptosomes in a VGF dependent manner

To explore the molecular mechanism underlying BDPP's antidepressant actions, we examined abundance of GluR1 in dHc synaptosomes obtained from an independent cohort of naive AAV-GFP- or AAV-Cre-injected *Vgf*$^{ff/ff}$ mice (without behavioral assessment) 17 days after the initiation of BDPP or water treatment (Figure 4A). BDPP treatment up-regulated GluR1 levels in dHc synaptosomes in AAV-GFP-injected mice but this effect was blocked in AAV-Cre-injected mice (Figure 4B, C).

Dorsal hippocampal BDNF expression is required for the antidepressant efficacy of BDPP treatment

To determine whether BDNF expression in dorsal hippocampus (dHc) is required for the antidepressant effects of BDPP, we treated AAV-Cre or AAV-GFP-injected floxed BDNF mice (homozygotes designated *Bdnf*$^{flox/flox}$) with BDPP or water for 17 days and subsequently assessed their behavioral phenotypes (Figure 5A). BDPP did not affect locomotor activity (Figure 5B), but induced antidepressant effects in dHc AAV-GFP-injected *Bdnf*$^{flox/flox}$ mice in the SST (Figure 5C) and FST (Figure 5D). However, these effects were completely absent in dHc AAV-Cre-injected *Bdnf*$^{flox/flox}$ mice, suggesting that dHc BDNF is required for the antidepressant actions of BDPP.

DISCUSSION

In the present study, we demonstrate that chronic BDPP treatment produces behavioral phenotypes that mimic those induced by antidepressant drugs[31] in naive mice. In addition, our results show that chronic BDPP treatment protects the mice from the detrimental effects of CVS. Many dietary polyphenols have been demonstrated to produce antidepressant effects [12]. Most recently, one study reported that chronic BDPP treatment alleviates chronic social defeat stress-induced social avoidance and two BDPP-derived metabolites, dihydrocaffeic acid (DHCA) and malvidin-3-O-glucoside (Malgluc) promote resilience by modulating synaptic plasticity and peripheral inflammation [14] With BDPP treatment administered in parallel with stress exposure, our current results suggest a preventive effect of BDPP on stress-induced depression. However, further investigation will be required to determine whether BDPP treatment initiated after the end of stress exposure has the same beneficial effects as parallel treatment.

Dorsal hippocampus has been demonstrated to be sensitive to stress and antidepressant treatments. Various stress paradigms have been shown to cause synaptic dysfunction and decrease BDNF levels [32,33] while antidepressant treatments reverse these changes in dorsal hippocampus [34] Here, we show that BDPP treatment upregulates VGF expression in dorsal hippocampus of naive mice. Our current results are consistent with previous studies demonstrating that hippocampal VGF is upregulated by antidepressant treatments such as imipramine, exercise and ketamine[17,19,20]. Once ingested, polyphenols in BDPP are metabolized by microbiota in the intestine, producing an extensive array of phenolic metabolites [13,35]. Many of these metabolites could be found in brain, where they could activate cAMP response element-binding protein (CREB) signaling in hippocampus [12]. The

vgf promoter contains a CREB binding site [15], suggesting that BDPP-induced VGF expression could be potentially regulated by CREB signaling. Polyphenols have been reported to render their beneficial effects by modulating neuroplasticity such as synaptogenesis and neurogenesis [36,37], which could be potentially mediated by the induction of VGF. Indeed, VGF C-terminal peptides, such as TLQP-62 and AQEE-30, have been demonstrated to facilitate dendritic maturation [38], enhance synaptic transmission [21], upregulate synaptic plasticity-related genes [19] and promote proliferation of neural progenitor cells [23].

We recently reported that antidepressant agents such as ketamine increase GluR1 levels and produce antidepressant-like phenotypes, and that these effects are blocked by VGF ablation in dorsal hippocampus [17] Our current results show that dorsal hippocampal VGF knockdown abolishes the antidepressant effects of BDPP, indicating that VGF expression in dorsal hippocampus is required for the actions of BDPP. GluR1 expression is downregulated in dorsal hippocampus by chronic stress [25] and GluR1 knockout mice manifest depression-like phenotypes [24]. Conventional antidepressant drugs [39,40], the rapidacting antidepressant agent ketamine [17] and dietary polyphenols [41] have been shown to promote GluR1 phosphorylation at Ser845. As phosphorylation of GluR1 at Ser845 controls the synaptic trafficking and incorporation of GluR1-containing AMPA receptor [42], many of these antidepressant agents increase GluR1 levels in the membrane, in synaptosomal preparations [18,26,27]. Our results show that BDPP increases GluR1 protein levels in dorsal hippocampal synaptosomes of controls but not in those mice with VGF ablated in this region, indicating that BDPP-induced synaptic GluR1 accumulation requires VGF.

BDNF plays an important role in regulating response to antidepressant treatments [43]. Forebrain BDNF conditional knockout and virus-mediated BDNF knockdown in hippocampus impair responses to conventional antidepressant drugs and/or ketamine [44–46] Our results show that BDNF knockdown in dorsal hippocampus attenuates antidepressant effects of BDPP, indicating that dorsal hippocampal BDNF expression is required for the actions of BDPP. Treatment with a number of botanical compounds is associated with increased levels of BDNF, phosphorylation of its receptor TrkB, and phosphorylation/activation of the transcription factor CREB [12,47–50]. Importantly, activated CREB is a known transcriptional regulator of VGF [51–53] and BDNF [54,55]. Although speculative based on our current data, and clearly requiring additional experimentation, this suggests the possibility that the VGF/BDNF autoregulatory feedback loop might play a more generalized role in polyphenol antidepressant and procognitive efficacy. It remains possible that in addition to effects on signaling molecules downstream of TrkB, including ERK, p70S6K, and mTOR (Fig. 6A), specific polyphenols could potentially induce epigenetic modifications to increase VGF and/or BDNF expression in specific brain regions, thereby initiating the VGF/BDNF autoregulatory cascade (Fig. 6B). For example, polyphenol administration to naive mice and those susceptible to repeated episodes of social defeat stress alters patterns of global DNA methylation in the central nervous system and periphery, and thus may promote resiliency to stress [56]. Of note, recent studies demonstrate that histone crotonylation and H3K27 trimethylation on the VGF promoter, driven by chromodomain Y-like protein (CDYL), are associated with transcriptional repression of VGF in mPFC and increased depression-like behavior [57].

In conclusion, our study confirms the antidepressant efficacy of BDPP. We propose that VGF-mediated synaptic GluR1 accumulation in dHc could potentially be the molecular mechanism underlying BDPP's actions.

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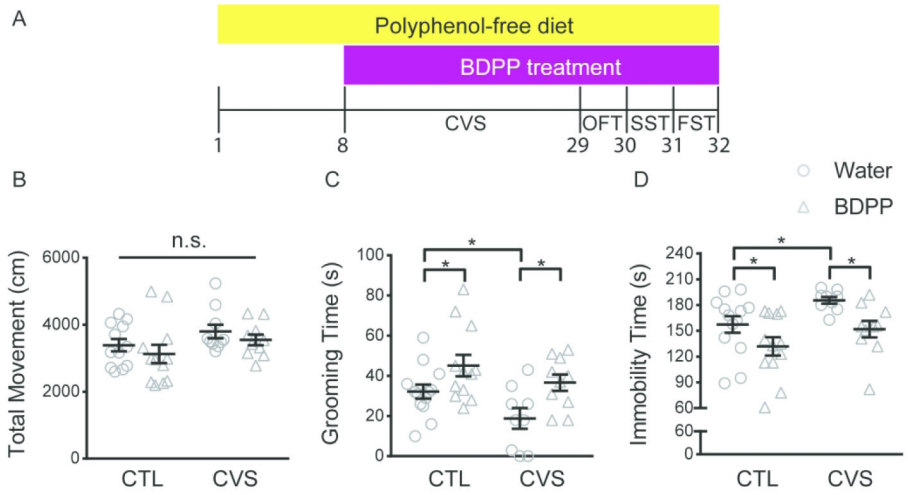

Figure 1.

BDPP treatment produces antidepressant effects in both naive and stressed mice. (**A)** Timeline of chronic BDPP treatment, chronic variable stress and behavioral tests. (**B)** BDPP treatment did not affect the locomotor activity in naive and stressed mice (**C**) BDPP treatment significantly increased grooming time in the SST in naive mice and averted reduction in grooming time in stressed. (**D)** BDPP treatment significantly decreased immobility time in the FST in naive mice and averted increase in immobility time in stressed mice, n = 9 ~ 13 per group. All data are presented as mean ± s.e.m. Two- way analysis of variance followed by Fisher's LSD test for B-D (* $P < 0.05$). OFT open field test, SST sucrose splash test, FST forced swim test.

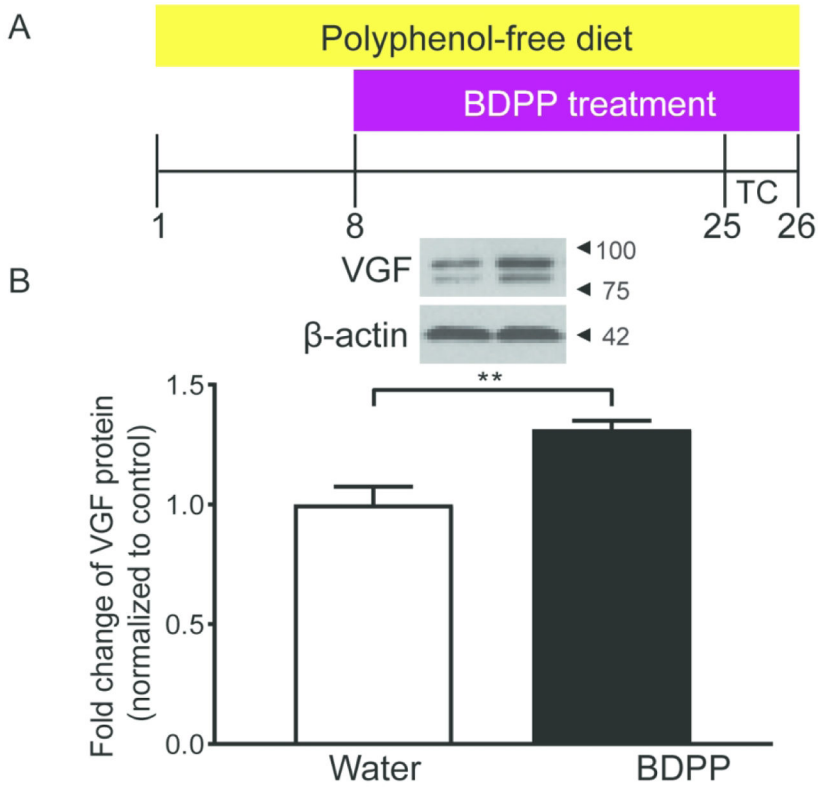

Figure 2.

BDPP treatment increases VGF expression in dorsal hippocampus of naive mice (**A)** Timeline of chronic BDPP treatment and tissue collection time points. (**B**) VGF protein levels were significantly up-regulated by BDPP treatment, n = 5 per group. All data are presented as mean ± s.e.m.. Student's t test for B (** $P < 0.01$). TC tissue collection.

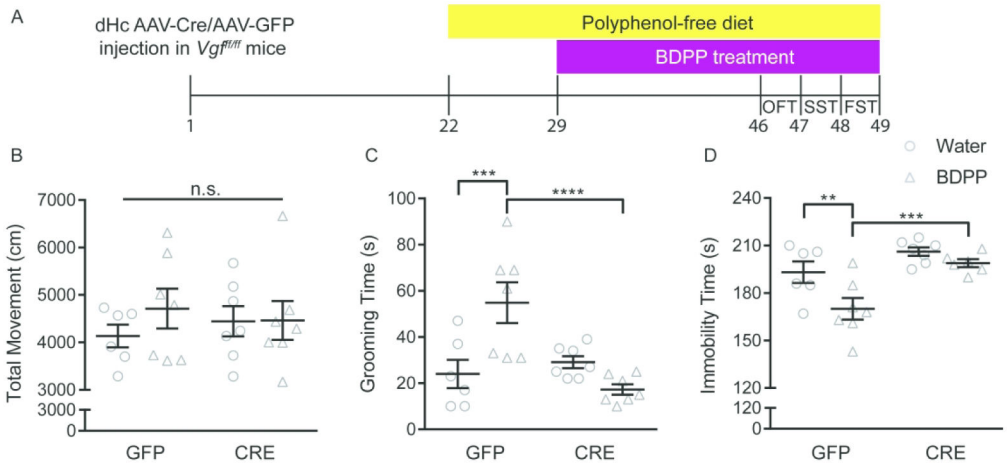

Figure 3.

Dorsal hippocampal VGF expression is required for the antidepressant actions of BDPP. **(A)** Timeline of stereotaxic surgery, chronic BDPP treatment and behavioral tests. (**B)** BDPP treatment did not affect the locomotor activity in dHc-AAV-GFP- and dHc-AAV-Cre-injected *Vgf*$^{fl/fl}$ mice. (**C**) BDPP treatment significantly increased grooming time in the SST in dHc-AAV-GFP- but not dHc-AAV-Cre-injected *Vgf*$^{fl/fl}$ mice(**D)** BDPP treatment significantly reduced immobility time in the FST in dHc-AAV-GFP- but not dHc-AAV-Cre-injected *Vgf*$^{fl/fl}$ mice, n = 6 ~ 7 per group. All data are presented as mean ± s.e.m.. Two-way analysis of variance followed by Fisher's LSD test for B-D (**P < 0.01, *** P < 0.001, **** P < 0.0001). OFT open field test, SST sucrose splash test, FST forced swim test.

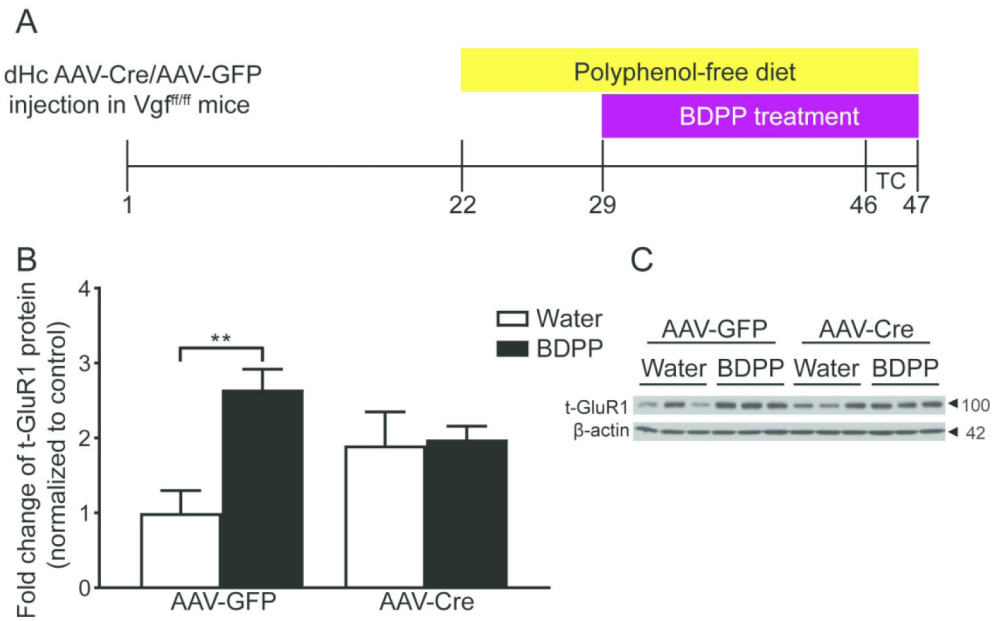

Figure 4.

Dorsal hippocampal VGF expression is required for increased total GluR1 abundance in synaptosome induced by BDPP. **(A)** Timeline of chronic BDPP treatment and tissue collection time points. (**B**) The total abundance of GluR1 was significantly increased in synaptosomes of AAV-GFP-injected but not AAV-Cre-injected *Vgf*$^{ff/ff}$ receiving BDPP treatment. (**C**) Representative western blot images of data shown in B. n = 3 ~ 4 per group. All data are presented as mean ± s.e.m.. Two-way analysis of variance followed by Fisher's LSD test for B (** $P < 0.01$). TC tissue collection.

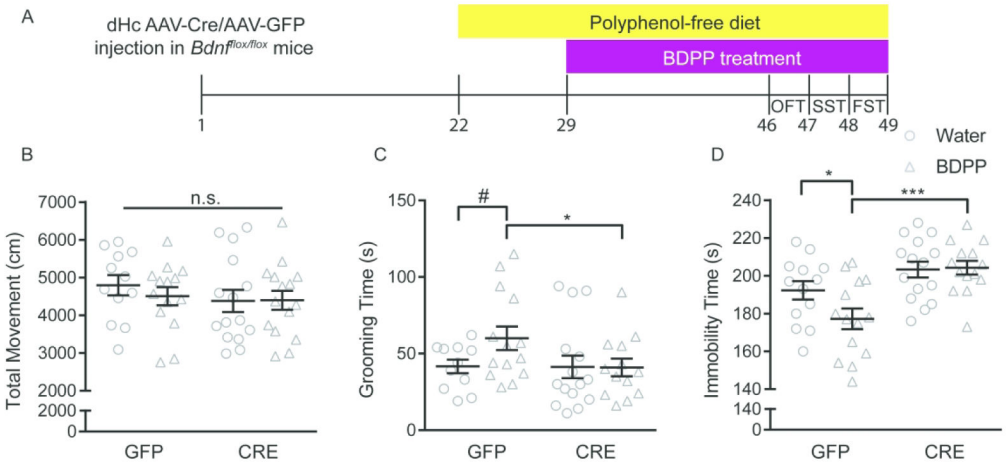

Figure 5.

Dorsal hippocampal BDNF expression is required for the antidepressant actions of BDPP (**A)** Timeline of stereotaxic surgery, chronic BDPP treatment and behavioral tests. (**B**) BDPP treatment did not affect the locomotor activity in dHc-AAV- GFP- and dHc-AAV-Cre-injected *Vgf*$^{ff/ff}$ mice. (**C**) BDPP treatment significantly increased grooming time in the SST in dHc-AAV-GFP- but not dHc-AAV-Cre-injected *Bdnf*$^{flox/flox}$ mice. (**D)** BDPP treatment significantly reduced immobility time in the FST in dHc-AAV-GFP- but not dHc-AAV-Cre-injected *Bdnf*$^{flox/flox}$ mice, n = 11 ~ 15 per group. All data are presented as mean ± s.e.m.. Two-way analysis of variance followed by Fisher's LSD test for B-D (# P = 0.0693, * P < 0.05, *** P < 0.001). OFT open field test, SST sucrose splash test, FST forced swim test.

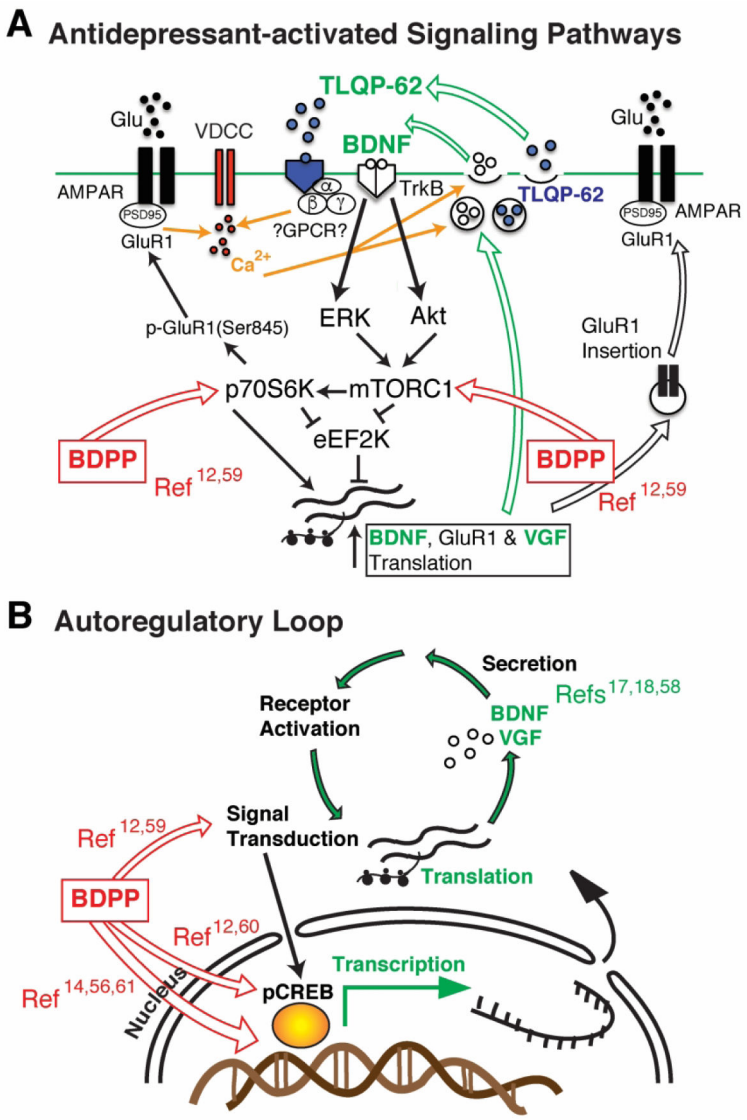

Figure 6.

Potential involvement of a VGF/BDNF/TrkB autoregulatory feedback loop in the antidepressant actions of BDPP. In panel A, BDNF/TrkB and VGF signaling pathways that hypothetically could contribute to the antidepressant responses to BDPP are shown, based on our results in Figs. 3 and 5 that demonstrate requirements for VGF and BDNF expression (highlighted in green), respectively, in dHc, in BDPP antidepressant efficacy. As has been suggested in previous studies of rapid-acting antidepressants (e.g. ketamine)[17,18,58], secretion of TLQP-62, shown binding to a putative, currently unidentified GPCR, is postulated to trigger BDNF secretion, increasing BDNF/TrkB signaling and relieving translational suppression via mTOR and/or eEF2 pathways, as does ketamine [46]. BDPP has previously been shown to activate mTOR and p70S6K signaling pathways (indicated by red arrows)[59], and to increase levels of activated CREB [12], a critical transcriptional regulator of VGF [51–53] and BDNF [54,55]. Panel B illustrates potential mechanism(s) underlying BDPP antidepressant actions (indicated by the red arrows), which initially could involve

modulation of signal transduction pathways, particularly those that regulate translation (e.g. ERK, p70S6K, mTOR, and 4E-BP1)[12,59], activation of transcription factors (e.g. pCREB and c-Fos)[12,60], and epigenetic regulation (e.g. DNA methylation)[14,56,61]. We postulate that BDPP treatment impacts one or more of these pathways, resulting in activation of the VGF/BDNF/TrkB autoregulatory feedback loop (highlighted in green), leading to increased transcription, synthesis and/or secretion of VGF and BDNF, increased synaptic plasticity, and antidepressant behavioral effects.

Additional abbreviations: cAMP-response element-binding protein (CREB); eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1); mammalian target of rapamycin (mTOR); ribosomal protein S6 kinase β-1 (p70S6K); voltage-dependent calcium channel (VDCC). Numbered references in the figure refer to published studies we cite that identify specific pathways that are activated by BDPP.