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Chronic histamine 3 receptor antagonism alleviates depression like conditions in mice via modulation of brain-derived neurotrophic factor and hypothalamus-pituitary adrenal axis

Ajeet Kumar[a], Shalini Dogra[a], Chandan Sona[a,b], Deepmala Umrao[a], Mamunur Rashid[c], Sandeep K Singh[c], Muhammad Wahajuddin[c], Prem N Yadav[a,b,*]

[a] Pharmacology Division, CSIR-Central Drug Research Institute, Lucknow, 226031, India
[b] Academy of Scientific and Innovative Research (AcSIR), New Delhi, 110025, India
[c] Division of Pharmaceutics and Pharmacokinetics, CSIR-Central Drug Research Institute, Lucknow, 226031, India

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ABSTRACT

The last two decades of research has established histamine (HA) as a neurotransmitter. Since H3R antagonists are known to modulate several neurotransmitters besides HA, H3R antagonists have shown potential for the treatment of different central nervous system disorders, including depression. However, molecular mechanisms underlying the beneficial effects of H3R antagonism in depression are not clear, yet. In the present study, we investigated the antidepressant potential of ciproxifan, a selective H3R antagonist, in chronic unpredictable stress (CUS) model of depression in C57BL/6 J mice. We observed that chronic treatment of CUS mice with ciproxifan (3 mg/kg *i.p.*; for three weeks) alleviates depression-like symptoms such as helplessness measured by forced swim and tail suspension test (FST and TST), anhedonia measured by sucrose preference test (SPT) and social deficit measured in social behavior test. Chronic ciproxifan treatment restored CUS induced BDNF expression in the prefrontal cortex (PFC) and hippocampus. We also observed that ciproxifan modulates CUS induced NUCB2/nesfatin-1 and CRH expression in the hypothalamus and plasma corticosterone. We also determined the direct effect of HA on BDNF expression in neurons by western blotting and immunocytochemistry, and found that HA significantly induced BDNF expression, which was blocked by the H4R selective antagonist, but not by other HA receptor selective antagonists. Furthermore, ciproxifan significantly modulated NMDA glutamate receptor subunits NR2B and NR2A. Thus, these results suggest that increased HA signaling in the brain produces antidepressant-like effects in mice and modulates BDNF expression and HPA-axis.

1. Introduction

Modulation of histaminergic activity has been shown to be involved in several physiological functions, such as circadian rhythm, energy homeostasis, sensory and motor functions, cognition, and attention, which are affected in several central nervous system (CNS) disorders (Haas and Panula, 2003; Leurs et al., 2005). All actions of histamine (HA) are orchestrated by four HA receptors, H1-H4R, which are members of the G-protein-coupled receptor (GPCR) family (Haas and Panula, 2003). Out of four HA receptors, H3R is of particular interest concerning CNS functions. H3R is a prime regulator of HA levels and is exclusively expressed in CNS (Esbenshade et al., 2008). This receptor is present on the pre-synapse of histaminergic neurons and acts as autoreceptors to regulate the synthesis and release of histamine (Arrang et al., 1987). In addition, activation of H3R has been shown to inhibit the release of many other important neurotransmitters, such as serotonin, norepinephrine, acetylcholine (Esbenshade et al., 2008), and therefore modulate various CNS functions, including cognition, emotion, stress, feeding, and nociception (Leurs et al., 2005). Given that H3R is a constitutively active receptor and expressed in the neuronal population of the cortex, hippocampus, hypothalamus, and striatum (Esbenshade et al., 2008; Lovenberg et al., 1999), significant efforts by both, academia and pharmaceutical companies, have been put into the development of therapeutics for the treatment of sleep disorder, cognitive impairment, obesity and mood disorders (Shan et al., 2015). In spite of several efforts over past decades, only one H3R antagonist Pitolisant has been approved for narcolepsy so far (Szakacs et al., 2017).

Chronic stress over activates hypothalamic-pituitary-adrenal (HPA)

* Corresponding author at: Pharmacology Division, CSIR-Central Drug Research Institute, Lucknow, UP, 226031, India.
E-mail address: pn.yadav@cdri.res.in (P.N. Yadav).

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axis activity, which is widely known to increase anxiety and depression-like behaviors in human as well as rodents. Although intracerebroventricular (*i.c.v.*) infusion of HA in rats has been shown to increase mRNA expression of corticotropin-releasing hormone (CRH), arginine vasopressin, and oxytocin in the paraventricular nucleus (PVN) of hypothalamus (Knigge et al., 1999), several other studies showed decreased brain HA signaling and/or levels in depression-like conditions (Femenia et al., 2015; Perez-Garcia et al., 1999; Taylor and Snyder, 1971). Furthermore, a recent study in the Flinders Sensitive Line of rat, a preclinical model of depression with impaired memory, showed antidepressant and pro-cognitive effects of Clobenpropit, an H3R antagonist (Femenia et al., 2015). Also, two non-imidazole H3R antagonists have also been shown to exhibit the antidepressant-like effect in rodents (Bahi et al., 2014; Gao et al., 2013). However, the mechanisms underlying the antidepressant action of H3R antagonists are poorly understood, especially in the context of stress-induced depression-like conditions. Since around 40% of the depressed patients do not respond to currently available antidepressants, including serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), the impetus for discovering alternative approaches beyond SSRIs & SNRIs is compelling. Although emerging pharmacological evidence stated above posit H3R antagonism as a new promising approach, unlike the SSRIs and SNRIs, the effects of H3R antagonists on widely known molecular determinants of depression such as brain-derived neurotrophic factor (BDNF), *N*-methyl-D-aspartate receptor (NMDAR) subunits and NUCB2/nesfatin-1 are not known (Emmerzaal and Kozicz, 2013; Sanacora et al., 2008).

The present study was undertaken to unravel the molecular mechanisms involved in the antidepressant actions of H3R antagonism. We demonstrated that three weeks of chronic unpredictable stress (CUS) induced depression-like symptoms in C57BL/6 J mice, which was reversed by systemic treatment with ciproxifan, an H3R antagonist. Further mechanistic studies in brain tissue and primary cortical neurons revealed that chronic H3R antagonist treatment modulates BDNF expression and normalizes perturbed HPA axis due to CUS. This study for the first time provides molecular insights in antidepressant action of H3R antagonism in mice.

2. Materials and methods

2.1. Animals

All in vivo experiments and procedures were performed in accordance with the guidelines established in the guide for the care and use of laboratory animals and were approved by the Institutional Animal Ethics Committee (IAEC) of CSIR-Central Drug Research Institute, Lucknow, India. The IAEC is certified by Animal Welfare Board of India (AWBI) and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), which are statutory bodies of Government of India. Male C57BL/6 J mice (6–8 weeks old) weighing 22–25 g were housed in cages with dimension 29 × 22 × 14 cm (floor area ~600 cm^2). Animals were housed in the group (6 mice /cage) on a 12 h light/dark cycle (lights on at 8.00 a.m.) and room environment was strictly controlled at the temperature (22 ± 2°C) with 50–70% humidity. Food (maintenance diet pellets, Altromin International, Germany, Cat. No. 1320) and water (autoclaved sterile) were provided ad libitum.

2.2. Drugs

Ciproxifan maleate was purchased from Sigma-Aldrich. For in vivo experiments, ciproxifan was dissolved in normal saline and administered via *intraperitoneal* injections (*i.p.*) at the dose of 3 mg/kg body weight of mice once daily. All behavior experiments were performed after 15–16 h of ciproxifan treatment as shown in Fig. 1A. For in vitro experiments histamine, (endogenous ligand of histamine receptor), triprolidine hydrochloride (H1R antagonist), ranitidine hydrochloride (H2R antagonist) and ciproxifan maleate (H3R antagonist) were purchased from Sigma-Aldrich and JNJ 7777120 (H4R antagonist) from Tocris Biosciences, UK. All drugs for in vitro studies were dissolved in cell culture grade Dimethyl Sulfoxide (DMSO) to prepare stock solutions of 10 mM, which were further diluted in the culture media to the desired dilutions, and appropriate vehicle controls were used in every experiment.

2.3. Behavioral procedure

All behavioral experiments were performed in normal healthy C57BL/6 J mice accordance with the guidelines established in the guide for the care and use of laboratory animals and were approved by the Institutional Animal Ethics Committee (IAEC) of CSIR-Central Drug Research Institute, Lucknow, India. In this study, we used total 103 C57BL/6 J mice for four individual experiments as described in supporting data Table S1. All behavioral experiments were performed only after 14–16 h of the ciproxifan treatment during 9:00 a.m. to 5:00 p.m. We have used the same cohort of mice for more than one behavioral tests and the order of these tests have been given in Fig. 1A.

2.3.1. Chronic unpredictable stress (CUS)

CUS paradigm was performed as described previously with some modifications (Ducottet et al., 2003), (Ibarguen-Vargas et al., 2008).The C57BL/6 J mice (6–8 weeks old and 22–25 g weight) were used to induce depression-like symptoms by CUS. Mice were subjected to two stressors each day for three weeks. To avoid adaptation, the stressors were randomized and chosen from seven different types of stressors (Supp Table S2): five-minute water swim stress, reversal of 12 h light/dark cycle, restraining stress for 60 min, overcrowding for overnight, cold stress for 60 min at 4°C, overnight wet bedding and cage tilt at 45°. All stressors of CUS procedure were applied on mice in animal housing room, except reversal of light/dark cycle, which was performed in a separate procedure room with the same environmental conditions. Mice subjected with CUS and control mice were separately housed in the group (6 mice/cage), and behavioral experiments were performed after 24 h of the last stress exposure. The immobility time in forced swim test (FST) was measured to determine the depression-like symptoms in mice before (first FST to determine the baseline immobility time) and after (the second FST to identify susceptible mice) the three weeks CUS exposure. Only susceptible mice (55–60% of CUS exposed mice) that exhibited the significant increase in immobility time in second FST compare to first FST were selected for further study with the H3R antagonist.

2.3.2. Forced swim test (FST)

FST is a behavioral test to measure the behavioral despair in mice. FST was performed according to the protocol (Dogra et al., 2016). In brief, mice were put in a glass cylinder (14 cm diameter, 25 cm height), containing water at the level of 15 cm with temperature 24 ± 2°C. The fresh water was refilled between trials to maintain water temperature. The mice movements were recorded for 5 min and immobility time was determined by using AnyMaze 4.7 software (Stoelting, USA).

2.3.3. Tail suspension test (TST)

Tail suspension test was performed as described previously (Steru et al., 1985). TST was performed 24 h after the forced swim test. For TST, mice were suspended on the rod 58 cm above platform by an adhesive tape, placed approximately 1 cm from the tip of the tail. Mice were allowed to hang for 330 s, and the duration of immobility was recorded during the last 300 s of the test by AnyMaze 4.7 software (Stoelting, USA). Mice were considered immobile only when they hung passively and completely motionless.

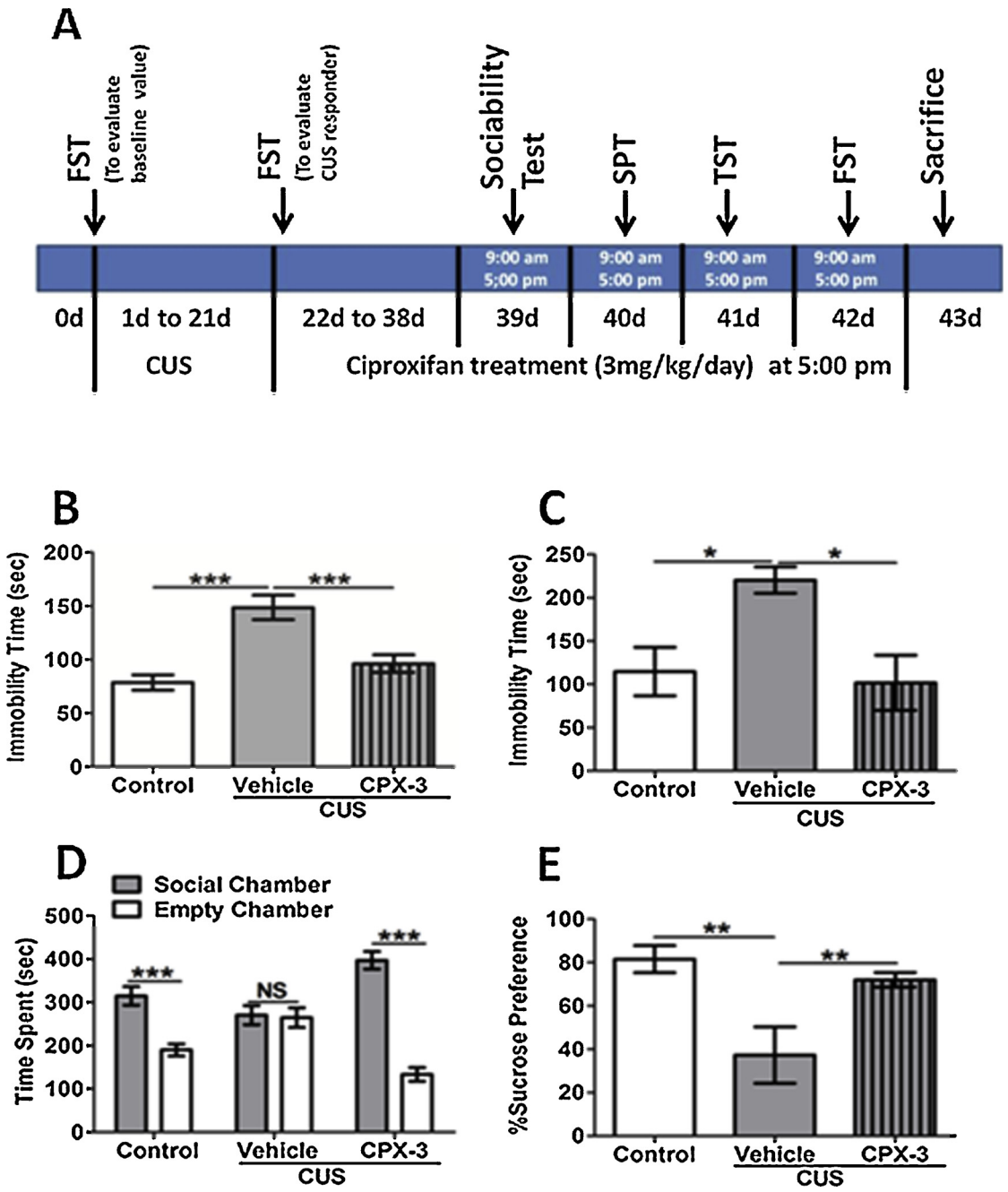

Fig. 1. Chronic treatment of ciproxifan alleviates CUS induced depression-like symptoms in mice. (A) Diagram showing the timeline of drug treatment and behavioral assays (B) Bar graph (mean ± SEM) showing immobility time in forced swim test with control and CUS subjected mice treated with vehicle or ciproxifan (3 mg/kg, *i.p.*for three weeks) ***$p < 0.001$; one-way ANOVA, N = 13-19/group. (C) Bar graph (mean ± SEM) showing immobility time in tail suspension test of CUS subjected vehicle-treated mice versus control mice or ciproxifan treated CUS subjected mice. *$p < 0.05$; one-way ANOVA, N = 4-5/group. (D) Bar graph (mean ± SEM) showing time spent in social chamber versus empty chamber of control mice and vehicle or ciproxifan treated CUS subjected mice. ***$p < 0.001$; two-way ANOVA, N = 11-13/group. (E) Bar graph (mean ± SEM) showing percent sucrose preference of vehicle-treated CUS subjected mice versus control mice or ciproxifan treated CUS subjected mice in sucrose preference test. **$p < 0.01$; one-way ANOVA, N = 5-7, CPX-3 = ciproxifan 3mg/kg/day.

2.3.4. Social behavior test

Social behavior of test animals was tested using a social behavior test box as described previously with minor modifications (Moy et al., 2007). In brief, a three-chambered box was used where mice were given a choice to stay in the center chamber or spending time in the one side chamber with an unfamiliar mouse in a wired cage (Social chamber), or in the other side chamber with empty wired cage (Empty chamber). Before the sociability test, all mice were habituated to the arena by allowing them to explore all three chambers for 10 min. After habituation, the mouse was enclosed in the central chamber, and an unfamiliar mouse (C57BL/6 J) was enclosed in the social chamber. After that, the test mouse was placed in the center chamber and allowed to explore all the chambers for 10 min. The exploratory behaviors of mice were video recorded and time spent in each chamber was analyzed by AnyMaze 4.7 software (Stoelting, USA).

2.3.5. Sucrose preference test (SPT)

This test was performed exactly as described previously (Dogra et al., 2016). To determine the sucrose preference, all animals were trained with two bottles, one with 1% sucrose solution (Sigma-Aldrich)

and another with water for 48 h and position of the bottles were reversed every 12 h to rule out any side preference. Before the test session, mice were water deprived for 5 h followed by single housing and adding two bottles (containing water or 1% sucrose solution) to their home cage for 2 h. The consumption of water or sucrose solution was estimated simultaneously in the control and experimental groups by weighing the bottles. Sucrose preference was calculated as a percentage of total liquid intakes during the two-hour test session.

2.4. Primary cortical neuronal culture

The primary cortical neuronal culture was performed as previously described (Dogra et al., 2016). In brief, cortices were gently dissociated from the brain of 0–1 day (P0 - P1) old mouse pups and digested with 0.1% solution of papain at 37°C for 20 min. The digestion reaction was stopped by adding 5% bovine serum albumin solution (prepared in Hank's Balanced Salt Solution, HBSS) and triturated 10–15 times to get a dissociated cells suspension, which was then spun at 200 g to get dissociated neuronal cell pellet. The neuronal cells were suspended in Neurobasal media supplemented with 2% B27 (Invitrogen, #17504) and 0.5 mM Glutamax (Gibco, #35050) and plated onto poly-L-lysine coated 12-well plate and incubated at 37 °C in a humidified atmosphere of 95% air and 5% CO_2. These primary cortical neurons were treated on 11–12 days in vitro (DIV).

2.5. Brain tissue isolation and western blotting

At the end of behavioral experiments, mice were euthanized after 24 h of last behavioral test by the overdose of an anesthetic (350 mg/kg of avertin). First, we performed thoracotomy to open the heart in anesthetized mice and then collected the blood from left ventricles. Brain tissues- prefrontal cortex (PFC), hypothalamus and hippocampus were rapidly micro-dissected after the decapitation of fully anesthetized mice and immediately snap-frozen in liquid nitrogen and stored at −80 °C till further use.

Western blotting of protein from the brain tissue samples and primary neurons was performed as described previously (Dogra et al., 2016). The western blotting was performed to analyze the protein expression in the brain tissue and primary neurons. Harvested brain tissues and the primary neurons were solubilized in the protein lysis buffer (25 mM Tris, pH 7.5; 10% Glycerol, 0.5% CHAPS, 0.5% sodium deoxycholate, 1% NP40, 150 mM NaCl, 1% SDS with protease inhibitor cocktail and phosphatase inhibitor cocktail) for 30 min on ice and centrifuged to obtain clear soluble protein lysate. The protein concentration was estimated by bicinchoninic acid (BCA) method. Protein samples (50–60 µg) were subjected to 8 to 12% SDS-PAGE, and transferred to polyvinyl difluoride (PVDF) membrane. The membrane was blocked with blocking buffer (5% bovine serum albumin in 1X Tris-buffered saline) for two hours. After the blocking, the membrane was incubated overnight with specific primary antibodies (Supplementary Table S3 for details of each antibody used in this study) at 4 °C. Following overnight addition of primary antibody, the PVDF membrane was washed thrice and incubated with horseradish peroxidase (HRP) conjugated secondary antibodies for 60 to 90 min. Protein bands were visualized using a chemiluminescent (ECL) solution (Merck-Millipore, India) and gel documentation system (MyECL Imager, ThermoScientifc, USA). All quantifications were performed using MyImage analysis software (ThermoScientifc, USA).

2.6. Quantitative real-time PCR

For CRH mRNA expression analysis, hypothalamic tissue was processed for total RNA extraction using TRIzol (Invitrogen Corp.) as per manufacturer's instructions. In brief hypothalamic tissue from each mouse was homogenized with 0.5 ml TRizol reagent and removed the pellet (debris) after the centrifugation of lysate at 12,000 *g* at 4°C. After that, 0.1 ml of chloroform was added and mixed vigorously for 3 min followed by centrifugation at 12,000 *g*. Finally, RNA was precipitated by adding 0.25 ml isopropanol in the aqueous phase and centrifuged at 12,000 *g* for 10 min. RNA pellet obtained was solubilized in RNAase-free water. The amount of total RNA was quantified using NanoDrop 2000c spectrophotometer (Thermo Scientific), and cDNA was prepared using GeneSure First Strand-cDNA synthesis kit (Cat. No. PGK 162-B) according to the manufacturer's instructions. Quantitative polymerase chain reaction (qPCR) was performed with DyNAmo ColorFlash SYBR Green qPCR Kit (Cat. No. F416S, Thermo Scientific) using QuantstudioTM 12 K Flex Real-Time PCR System (Applied Biosytems). Relative gene expression was estimated by calculating the ΔΔCT. The following primer sequences were used: CRH forward: 5′-CGGCTAACT TTTTCCGCGTG-3′ reverse: 5′-CTGAGCTAACTGCTCTGCCCG-3′andβ-actin, forward: 5′-TGTTACCAACTGGGACGACA-3′ reverse: 5′-CTGGGT CATCTTTTCACGGT-3′.

2.7. Immunocytochemistry (ICC)

ICC experiments were performed according to the previously described method (Dogra et al., 2016). Primary cortical neurons grown on poly-L-lysine coated coverslips at DIV 12 were fixed with 4% para-formaldehyde (PFA) solution for 10 min at 4°C and incubated with blocking buffer containing 3% BSA, 3% horse serum, 0.3% Triton X100 (in 1X PBS) for two hours at room temperature, followed by incubation with primary antibodies (Supplementary Table S1) for 18 h at 4°C. After that, secondary antibodies conjugated with the fluorophore were added for 90 min at room temperature followed by three washes with PBST (0.3% Triton X100 containing PBS) and coverslips were mounted on glass slides using Vectashield mounting medium (Cat. No. H-1000, Vector Laboratories). Fluorescence signals were captured under Leica DMI6000 microscope using 20X objective. Quantification of fluorescence signals was done by ImageJ software, and arbitrary fluorescence units were normalized using MAP2 signals in each image. Cropped images were assembled for presentation in Adobe Photoshop (version 7.1).

2.8. Corticosterone ELISA

Blood samples were collected by cardiac puncture from the left ventricle of anesthetized mice after 14–16 h of the last behavioral experiment. Since a previous study reported that corticosterone level fluctuated with the circadian manner and more stable at daytime (10:00 to 12:00) (Oishi et al., 2006), we collected all blood sample at daytime between 11:00 a.m. and 2:00 p.m. to avoid variations due to circadian corticosterone oscillations. Blood plasma isolated by centrifugation of blood samples (with anticoagulant) at 1500 *g* and stored at −80 °C till further use. Corticosterone levels were measured in blood plasma using ELISA kit (Arbor Assays, Cat No K014-H1) following manufacturer's instructions. In brief 50 µl of dissociated and diluted plasma samples or standards in IgG coated assay plate. After that, 25 µl of the corticosterone conjugated with peroxidase was added in each well followed by addition of 25 µl of the DetectX corticosterone antibody and further incubated for at room temperature for 1 h. Solutions from each well were aspirated, and the plate was washed four times followed by addition of Tetramethylbenzidine (TMB) substrate (100 µl/well) incubation for 30 min at room temperature to develop the color. Absorbance was determined at 450 nm after stopping the reaction with 50 µl of the stop solution. Data were analyzed using the online software (www.myassays.com/arbor-assay-corticosterone-enzyme-immunoassay-kit.assay).

2.9. Statistical analysis

Statistical analysis was performed using GraphPad Prism 5 software. Experimental data having three or more unmatched group with means

(FST, TST, SPT, protein expressions, and corticosterone data) were analyzed by one-way analysis of variance (ANOVA) followed by Newman-Keuls *post hoc* test. Social behavior data were analyzed using two-way ANOVA followed by Bonferroni *post hoc* test to determine the response of treatment groups in social chamber versus empty chamber. We used the unpaired *t*-test to compare the means of two groups. $p < 0.05$ was considered as significant, and $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ were used to denote significance level between the group.

3. Results

3.1. Ciproxifan alleviates CUS-induced depression-like symptoms in mice

To determine the effects of ciproxifan (a selective H3R antagonist) on CUS-induced depression-like symptoms, brain uptake data of ciproxifan in mice (C_{max} = 999 ng/ml; Supp. Fig S1 and Table S4) and previously reported positron-emission tomography (PET) study in pigs (Plisson et al., 2009) clearly suggest that ciproxifan pass the blood-brain barrier (BBB) and reach the brain. C57BL/6 J mice were first subjected to seven randomized stressors for three weeks to develop depression-like symptoms. Before the treatment with ciproxifan, we measured behavioral despair to ensure if CUS paradigm we used was sufficient to induce depression-like symptoms, and indeed significant increase in immobility time in second FST compare to baseline FST (i.e., first FST) was observed (Supp. Fig. S2, $F_{2,\ 59} = 22.0$, $p < 0.001$; two-way ANOVA). However, we did not observe any significant change in that body weight of CUS exposed mice compare to before CUS exposure (Supp. Fig S3). These CUS subjected mice were then treated with ciproxifan (3 mg/kg, *i p.*) or vehicle for three weeks and after that evaluated in a battery of behavioral tests for depression-like phenotypes, i.e. FST, TST, sociability, and sucrose preference test (Fig. 1A). In concurrence to previous reports on other H3R antagonists (Bahi et al., 2014; Gao et al., 2013), ciproxifan also significantly reduced immobility time in FST (Fig. 1B, $F_{2,41} = 14.35$, $p < 0.001$; one-way ANOVA) and TST (Fig. 1C; $F_{2,\ 11} = 6.80$, $p < 0.05$; one-way ANOVA). Since social deficit is considered one of the cardinal signs of depression, we also evaluated the effect of ciproxifan (3 mg/kg, *i.p.*) on sociability by using three-chambered social behavior test. We observed that ciproxifan treatment completely restored social behavior of CUS mice by increasing time spent in the social chamber (Fig. 1D; $F_{2,\ 64} = 22.27$, $p < 0.001$; two-way ANOVA). In addition, the significant antidepressant-like effect of ciproxifan was observed in sucrose preference test by reducing anhedonia (Fig. 1E; $F_{2,\ 15} = 8.46$, $p < 0.01$; one-way ANOVA). Whereas, ciproxifan treatment (3mg/kg for three weeks) in control healthy mice did not exhibit the significant effect in FST and social behavior test (Supp. Fig S4). Furthermore, we did not find any significant change in overall locomotor response in an open field with ciproxifan treatment in CUS mice (Supp. Fig S5)

3.2. Chronic treatment with ciproxifan restores CUS-induced decrease of BDNF levels in PFC and hippocampus

Previous reports suggest decreased BDNF levels in the hippocampus and cortex of depressed individuals as well as rodent models of depression as a surrogate neurochemical marker of depression (Duman and Monteggia, 2006). Therefore, we also investigated the chronic effect of ciproxifan (21 days) on BDNF expression in PFC and hippocampus of CUS exposed mice. In agreement to previous reports (Nibuya et al., 1995), we also observed the significant reduction in BDNF expression in both PFC and hippocampus of CUS exposed animals (Fig. 2). Interestingly, we observed the CUS-mediated decrease in BDNF expression in PFC, which was restored to the normal level by chronic ciproxifan treatment (Fig. 2 A and B, $F_{2,\ 19} = 8.56$, $p < 0.05$; one-way ANOVA). We found the similar effect of ciproxifan on BDNF expression in the hippocampus as well (Fig. 2 C and D; $F_{2,\ 17} = 6.063$, $p < 0.05$; one-way ANOVA). We further determined the H3R expression in PFC and hippocampus of control and CUS subjected mice by WGA pull-down followed by western blotting but found no change in CUS subjected mice treated with vehicle or ciproxifan as compared to control mice (Supp. Fig S6). These results of H3R expression is in line with the previously reported clinical study that showed no change in H3R expression in the PFC and hippocampus of the depressed individuals (Jin et al., 2009). In the light of these results and a previous report showing the enhanced histamine turnover rate in ciproxifan treated mice brain (Ligneau et al., 1998), it is very likely that ciproxifan induced BDNF expression in the brain is mediated via the increased level of histamine.

3.3. HA induced BDNF expression is mediated through H4R in primary cortical neurons

Since all histamine receptors (H1-H4R) are known to be expressed in neurons of cortex, hippocampus, hypothalamus, and several other brain regions and H3R antagonists including ciproxifan increases HA level (Haas and Panula, 2003; Leurs et al., 1998; Passani and Blandina, 2011; Reiner and Kamondi, 1994), we were curious to know whether increased levels of histamine (due to H3R antagonism) or ciproxifan (H3R antagonist) itself responsible for restoration of BDNF expression in PFC and hippocampus of CUS exposed mice. Therefore, we used the primary cortical neuronal system to delineate the target receptor involved in modulation of BDNF expression. Firstly, we demonstrated expression of both H3R and H4R by ICC and western blotting in primary cortical neurons (Supp. Fig S7 and S8). We further characterized the functionality of these two receptors to induce canonical GPCR signaling such as the activation of extracellular signal-regulated kinases (ERK) in response to agonist. We observed significant and time-dependent stimulation of phosphorylated ERK1/2 (pERK1/2) expression by Imetit (1μM), a selective H3R agonist, (Fig. 3 A and B, $F_{3,\ 16} = 4.396$, $p < 0.05$; one-way ANOVA) and by VUF8430 (1μM), a selective H4R agonist (Fig. 3 C and D, $F_{3,\ 21} = 6.206$, $p < 0.01$; one-way ANOVA).

Since others have shown that H3R antagonist augments brain HA level due to blockade of the auto-inhibitory function of H3R (Passani and Blandina, 2011), we sought the direct effect of HA on the expression of BDNF in primary cortical neurons. We found significant induction of BDNF in response to HA (1 μM, for 18 h) as determined by western blotting (Fig. 4A and B; $t(5) = 4.769$, $p < 0.01$) and immunocytochemical staining in primary cortical neurons (Fig. 4C and D, $t(5) = 7.075$, $p < 0.001$). At the same time, we also evaluated the effect of histamine treatment on BDNF expression in primary astrocytes and microglia. We did not find any significant effect of histamine treatment on BDNF expression in primary glial cells microglia and astrocytes (Supp Fig S9 and S10). Thus, in vitro data neglected the possibility of other cells (glial cells) in the enhancement of BDNF expression in brain tissue after the ciproxifan treatment. To reveal which histamine receptor(s) is/are involved in the HA-induced expression of BDNF, we used receptor selective antagonists (triprolidine for H1R, ranitidine for H2R, ciproxifan for H3R and JNJ7777120 for H4R) in primary cortical neurons. Interestingly HA induced BDNF expression was blocked by JNJ7777120 (10 μM, 18 h; Fig. 4 E and F; $F_{2,\ 9} = 7.121$, $p < 0.05$; one-way ANOVA and Supp. Fig S11 A and B), but not by ciproxifan (10μM, 18h; Supp. Fig S11 A and B; $F_{3,\ 15} = 10.16$, $p < 0.001$; one-way ANOVA). In addition, neither triprolidine (10 μM, for 18h) nor ranitidine (10 μM, 18h) could block the effect of HA on BDNF expression in the primary cortical neurons (Supp. Fig S11 C and D; $F_{3,\ 24} = 6.798$, $p < 0.01$; one-way ANOVA). These results suggest that H4R is essential for HA-induced BDNF expression in neurons in vitro and possibly in vivo too.

3.4. Ciproxifan reversed stress-induced activation of HPA axis in C57BL/6 J mice

Considering the literature suggesting over activation of the HPA axis

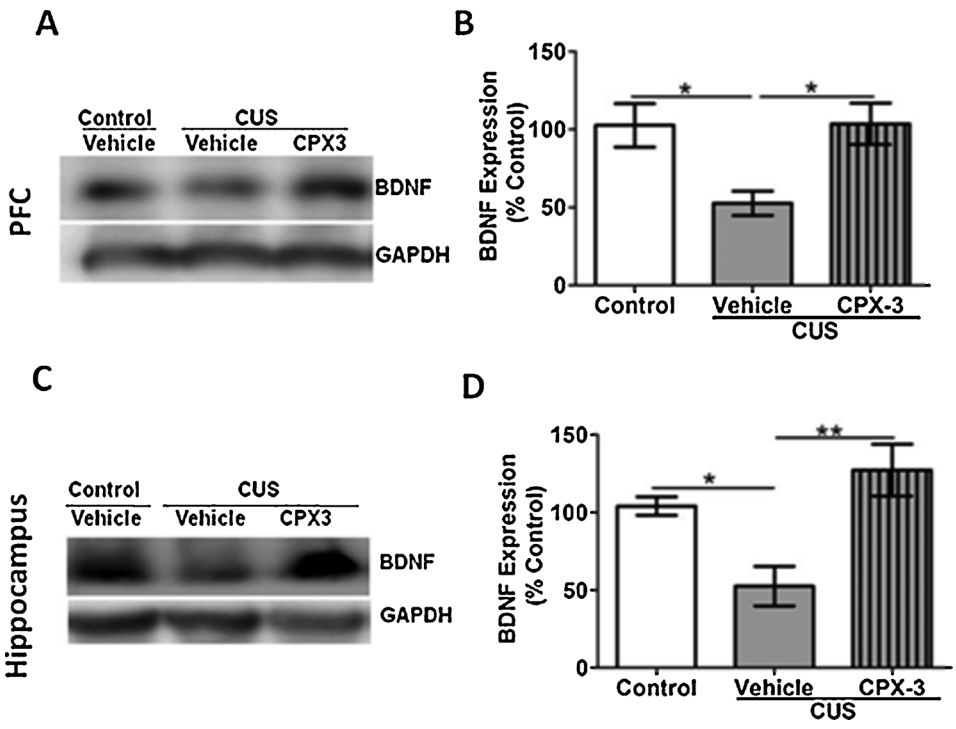

Fig. 2. Ciproxifan restores CUS mediated decrease of BDNF expression in the hippocampus and PFC. (A) Representative immunoblots and (B) bar graph (mean ± SEM) showing quantification of BDNF from PFC of vehicle-treated CUS exposed mice versus control mice or ciproxifan (CPX-3 = ciproxifan 3 mg/kg/day) treated CUS exposed mice $^{*}p < 0.05$; one-way ANOVA, N = 5-8/group. (C) Immunoblots and (D) quantification of BDNF from the hippocampus of vehicle-treated CUS exposed mice versus control mice, or ciproxifan treated CUS exposed mice $^{*}p < 0.05$, $^{**}p < 0.01$; one-way ANOVA, N = 7-8/group.

and involvement of brain NUCB2/nesfatin-1 in the pathophysiology of depression (Dore et al., 2017; Ge et al., 2015; Xu et al., 2017), we also determined the effect of H3R antagonist ciproxifan on NUCB2/nesfatin-1 and other molecular co-relates of perturbed HPA-axis in brain. We found that three weeks of CUS significantly increased hypothalamic NUCB2/nesfatin-1 expression in comparison to control mice (Fig. 5 A and B). Quite interestingly, chronic treatment with ciproxifan (3 mg/kg, *i. p.*, three weeks) significantly decreased NUCB2/nesfatin-1 expression in the hypothalamus (Fig. 5 A and B; $F_{2,\ 17} = 4.523$, $p < 0.05$; one-way ANOVA). Given that *i.c.v.* treatment of nesfatin-1 increases corticotrophin-releasing hormone (CRH) (Gotoh et al., 2013), we also measured the hypothalamic CRH mRNA expression after chronic treatment with ciproxifan CUS mice. We found that ciproxifan significantly decreased CUS-induced increase in CRH mRNA expression (Fig. 5 C; $F_{2,\ 14} = 5.73$, $p < 0.05$; one-way ANOVA). Similar to the effect of ciproxifan on CUS-induced NUCB2/nesfatin-1 and CRH expression in the hypothalamus, we also found that chronic treatment with ciproxifan significantly decreased CUS-induced plasma corticosterone level (Fig. 5D; $F_{2,\ 10} = 6.948$, $p < 0.05$; one-way ANOVA). These results suggest that ciproxifan (H3R antagonist) normalizes over activated HPA-axis in CUS exposed mice.

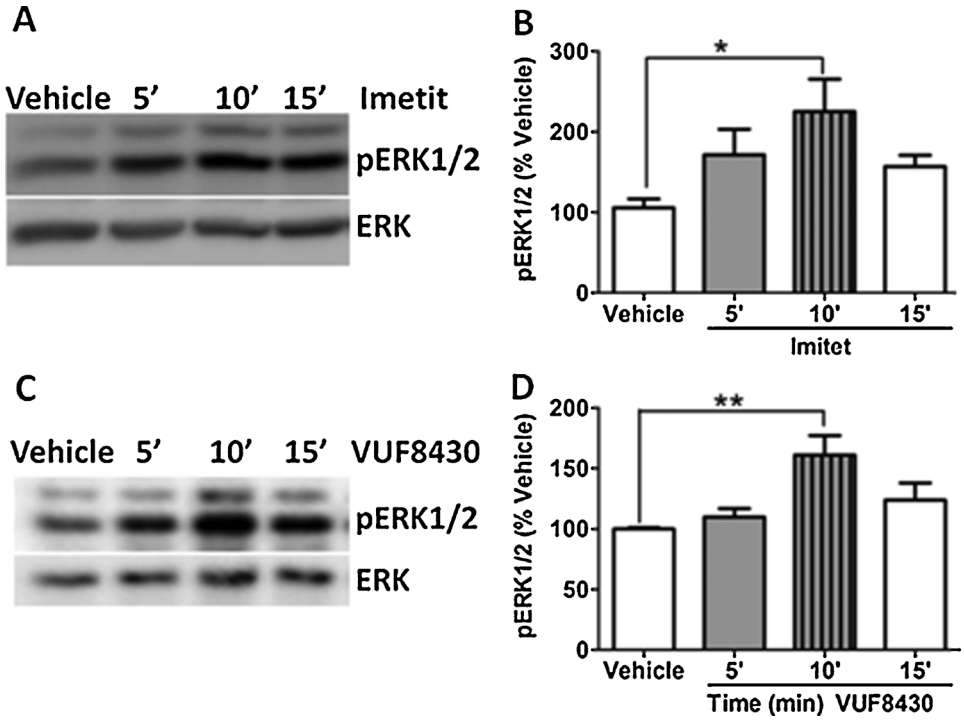

Fig. 3. Functional characterization of histamine 3 and 4 receptors (H3R and H4R) in primary cortical neurons. (A) Representative immunoblots and (B) quantification of pERK1/2 expression in the in primary cortical neurons treated with vehicle or Imetit (1 μM) for 5, 10 and 15 min $^{*}p < 0.05$; one-way ANOVA, N = 4-7/group. (C) Representative immunoblots and (D) quantification of pERK1/2 expression in the primary cortical neurons treated with vehicle or H4R agonist VUF8430 (1 μM) for 5, 10 and 15 min $^{**}p < 0.01$; one-way ANOVA, N = 6-7/group.

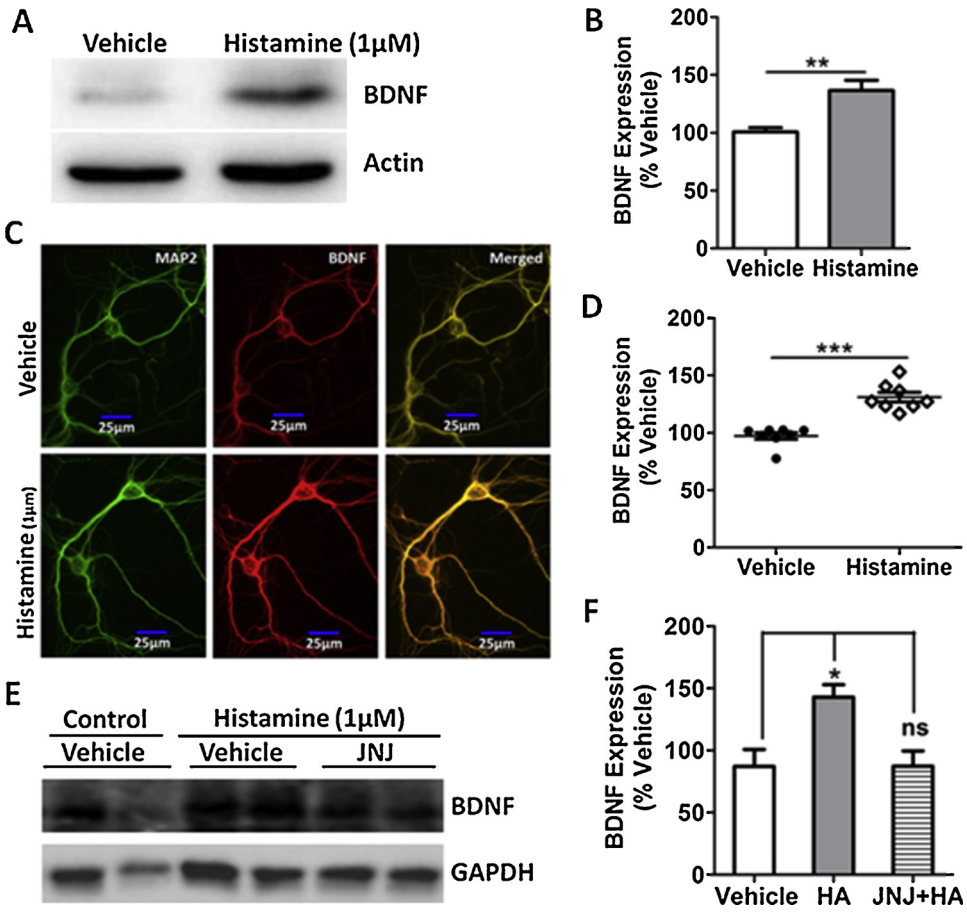

Fig. 4. Histamine-induced increased BDNF expression is blocked by the H4R antagonist in the primary cortical neurons. (A) Representative immunoblot and (B)quantification analysis of BDNF in the primary cortical neurons treated with histamine (1μM, 18 h) $^{**}p < 0.01$; *t*-test, N = 6-7/group.(C) Representative immunocytochemistry images and (D) quantification analysis of BDNF expression in the primary cortical neurons treated with histamine (1μM, 18h) in cortical neurons $^{***}p < 0.001$; *t*-test, N = 8/group. (E) Representative immunoblot and (F) quantification of BDNF expression in primary cortical neurons treated with histamine (HA = histamine, 1μM, 18h) either alone or along with H4R antagonist (JNJ = JNJ 7777120, 10 μM, 18h) $^{*}p < 0.05$, one way ANOVA, N = 4/group.

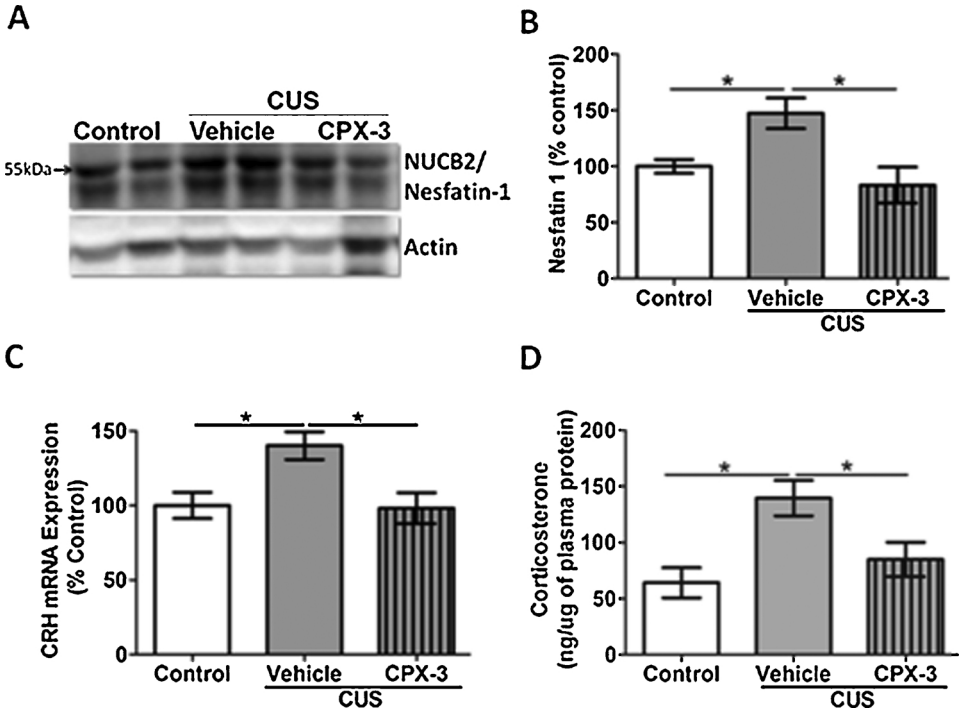

Fig. 5. CUS induced activation of the HPA axis is attenuated by H3R antagonism. (A) Representative immunoblots and (B) quantification analysis of NUCB2/nesfatin-1 in hypothalamic tissue of vehicle-treated CUS exposed mice versus control mice, or ciproxifan treated CUS exposed mice $^{*}p < 0.05$; one way ANOVA, N = 5-7. (C) Bar graph (mean ± SEM) showing hypothalamic CRH mRNA expression in control, and CUS exposed mice treated with either vehicle or ciproxifan (3 mg/kg), $^{*}p < 0.05$; one way ANOVA, (C). (D) Bar graph (mean ± SEM) showing plasma corticosterone level of CUS vehicle group versus control group or ciproxifan treated CUS group mice $^{*}p < 0.05$; one way ANOVA, N = 4-5, CPX-3 = ciproxifan 3mg/kg/day.

3.5. Ciproxifan treatment modulates NMDAR2A (NR2A) and NMDAR2B (NR2B) in Hippocampus

Since the multiple emerging lines of evidence implicate NMDA receptors in depression (Duman and Aghajanian, 2012; Sanacora et al., 2014; Skolnick et al., 1996), we investigated the effect of CUS on the expression of NR2A and NR2B subunits of NMDA ligand-gated ion channels in mice. We found that CUS exposed mice exhibited the significant decrease in the NR2B subunit expression, which was restored by chronic ciproxifan treatment (Fig. 6 A and B; $F_{2,\ 16} = 6.464$,

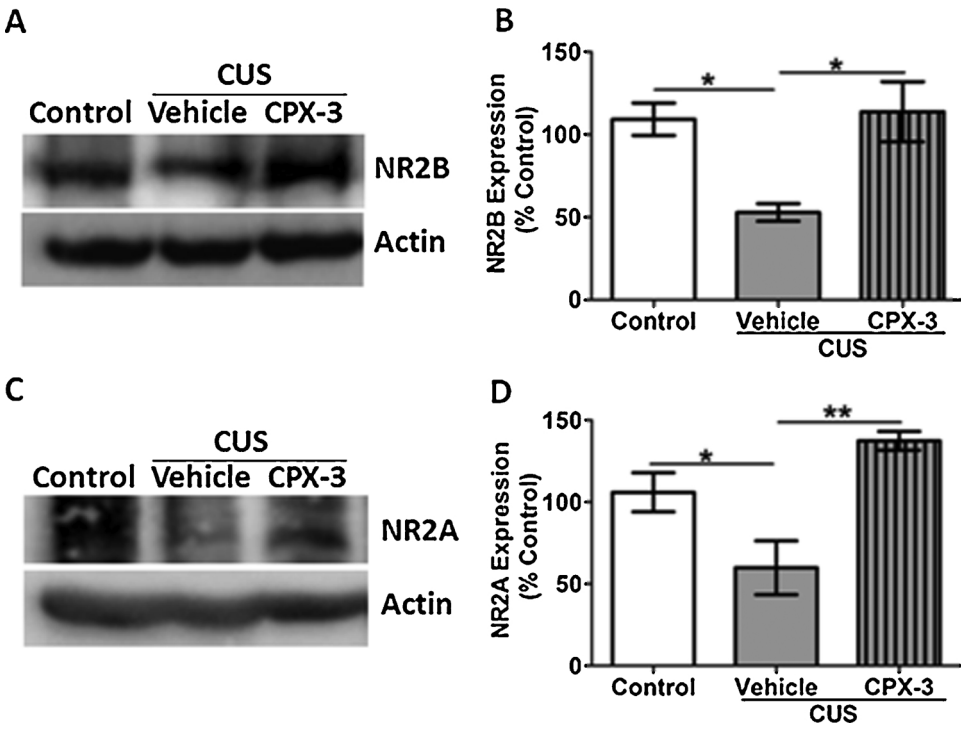

Fig. 6. CUS-induced decrease in NMDA receptor expression is attenuated by three weeks treatment of ciproxifan. (A) Representative immunoblots of NR2B expression in mice hippocampus tissue and (B) Quantification analysis of NR2B expression in hippocampus tissue of CUS exposed vehicle group versus control mice or ciproxifan treated CUS exposed mice $*p < 0.05$; one-way ANOVA. (C) Representative immunoblots of NR2A expression in mice hippocampus tissue and (D) Quantification analysis of NR2A expression from hippocampus tissue of CUS exposed vehicle mice versus control mice or ciproxifan treated CUS exposed mice$*p < 0.05$, $**p < 0.01$; one-way ANOVA.

$p < 0.01$; one-way ANOVA). In the same vein, NR2A subunit expression was also significantly decreased due to CUS, and chronic treatment with ciproxifan significantly up-regulated NR2A expression in the hippocampus compared to vehicle-treated CUS exposed mice (Fig. 6 C and D;$F_{2,\ 9} = 10.25$, $p < 0.01$; one-way ANOVA). However, no change was observed in NR1 subunit expression in the hippocampus of CUS mice (Supp. Fig S12 A and B).

4. Discussion

This study revealed that the chronic H3R antagonism alleviates chronic stress-induced depression-like condition and modulates stress-induced biochemical co-relates such as BDNF, corticosterone, NUCB2/nesfatin-1, and CRH in the brain. In this study, we used ciproxifan as the H3R antagonist, which have good brain availability as suggested by our brain uptake data (C_{max} 999.2 ng/ml) and previously reported PET imaging data (Plisson et al., 2009). Although previous rodent studies showed that acute treatment with H3R antagonist (30–45 minutes prior to behavioral assays) reduces the depression-like conditions (Bahi et al., 2014; Femenia et al., 2015), it is widely known that antidepressant effect by all the classes of currently approved drugs ensues only after 2–3 weeks due to readjustment of neurocircuits involved in depression. Thus, our results agree with widely established mechanisms of antidepressant action in preclinical as well as clinical settings (Machado-Vieira et al., 2010).

Several studies have shown reduced BDNF expression in PFC and hippocampus of CUS subjected mice, which were restored by antidepressants (Chourbaji et al., 2011; Duman and Monteggia, 2006; Willner et al., 2013). In agreement to previous reports, we also observed the significant reduction in BDNF expression in PFC and hippocampus after three weeks of CUS exposure, which was restored by the systemic administration of ciproxifan for three weeks. While CUS exposure/ciproxifan treatment did not show any effects on the expression level of H3R in PFC or hippocampus. Given the critical role of BDNF in mood and cognition, and our observation of ciproxifan and HA-induced BDNF expression in vivo and in vitro, respectively, the H3R selective antagonist could be useful for CNS disorders with mood and cognitive impairments. A recent study has reported that chronic treatment with S38093 (an H3R antagonist) restores BDNF mRNA expression in aged mice hippocampus supporting the procognitive functions of H3R antagonist (Guilloux et al., 2017). However, it is not clear which cell types (neurons or glial cells) were involved in the restoration of BDNF expression, and either H3R antagonist (S38093 in this case) directly restores BDNF expression or indirectly via increasing HA, which binds to other histamine receptor in the brain. To address this point, we used well differentiated primary cortical neurons (DIV 11–12), primary astrocytes (DIV 18–20) and microglia (DIV 10–12) to delineate the effect of HA on BDNF expression. Since HA did not show any effect on BDNF expression in glial cells, but HA induced BDNF expression in primary neurons was blocked by H4R antagonist only, clearly suggest that some of the beneficial effects of the H3R antagonist on mood and cognition may be mediated through H4R. However, further investigation with H4R selective agonist and antagonist administration in the brain is required to support this notion. Moreover, one electrophysiological study by Clapp and Luckman also showed that thioperamide (another inverse agonist of H3R) increased hypothalamic neuronal firing via increased HA action at postsynaptic H1 receptors (Clapp and Luckman, 2012). Actually, a recent study did show depression-like symptoms and cognitive impairments in H4R-knockout mice (Sanna et al., 2017), but didn't provide any mechanistic insight, such as BDNF expression in the brain. Besides, H3R antagonism has been shown to modulate several other neurotransmitters (Esbenshade et al., 2008), which in turn could modulate the BDNF expression. Thus, our results support the neuron-centric beneficial effect of H3R antagonism on mood in male mice. Further, multiple clinical and preclinical studies suggest that females are more susceptible to depression due to effects of gonadal hormones in stress response via regulation of serotonin, norepinephrine, and serum cortisol (Fernandez-Guasti et al., 2012; Goel and Bale, 2010; Kokras and Dalla, 2017; Monteggia et al., 2007). More importantly, previous reports suggest that cross-talk between hippocampal BDNF content and gonadal hormones plays important roles in vulnerability to stress induced depression (Autry et al., 2009) as well as in rescue of the emotional phenotype by environmental enrichment (Chourbaji et al., 2012). In this study however, we have investigated the antidepressant effects of ciproxyfan in male mice only, which limits the interpretation of antidepressant potential of H3R

antagonists.

Since the involvement of HPA-axis in anxiety and depression are well established. Nesfatin-1, an anorectic neuropeptide (Oh et al., 2006; Stengel and Tache, 2013) has been widely implicated in anxiety and depression-like behaviors as chronic or acute administration of nesfatin-1 increases depression-like symptoms, serum corticosterone and hypothalamic CRH mRNA expression (Bloem et al., 2012; Dore et al., 2017; Emmerzaal and Kozicz, 2013; Ge et al., 2015; Xu et al., 2017). However, the nature of the functional relationship between nesfatin-1 and HA signaling in the brain, and the effect of increased HA signaling on perturbed HPA axis is not clear. Our observation of CUS induced up-regulated NUCB2/nesfatin-1 expression in the hypothalamus, which correlated with depression-like conditions in mice further confirms the pro-depressive role of nesfatin-1 (Bloem et al., 2012; Emmerzaal and Kozicz, 2013; Ge et al., 2015; Xu et al., 2017). More importantly, our data for attenuation of hypothalamic NUCB2/nesfatin-1 expression by ciproxifan provides, for the first time, mechanistic insight for the beneficial effect of increased HA signaling in depression-like conditions. Although a study by Gotoh and colleagues (Gotoh et al., 2013) showed that acute *i.c.v.* treatment of histamine increases NUCB2/nesfatin-1 expression in the paraventricular nucleus (PVN), but not in the lateral hypothalamus, and suggests the reason for nesfatin-1 mediated anorexia; it is quite likely that increased HA signaling in PFC and hippocampus is responsible for its antidepressant action. Furthermore, several studies have shown that CUS increases plasma corticosterone, a biochemical marker of overactive HPA axis, and chronic treatment with antidepressants restores the corticosterone to the normal level (Pytka et al., 2017). In this context, our observation of the significant reduction of CUS-induced CRH mRNA expression in the hypothalamus and plasma corticosterone by ciproxifan, clearly supports our hypothesis that increased brain HA signaling resets HPA axis to normal and thereby modulates antidepressant mechanisms and pathways in PFC and hippocampus.

In the past decade, several clinical and preclinical findings suggest a significant role of glutamatergic signaling in the pathophysiology of depression (Duman and Aghajanian, 2012). In our study, we found three weeks of CUS exposure lead to a significant decrease in NR2A and NR2B expression in the hippocampus, which was normalized by the chronic treatment with ciproxifan. In the case of NR2A subunit expression, our result is consistent with previous reports (Femenia et al., 2015; Pacheco et al., 2017). However, our previous report (Dogra et al., 2016), and the CUS-induced decrease in NR2B expression in this study is opposite to what others have shown (Pacheco et al., 2017). This inconsistency may be due to the duration and severity of the stressor, as the region-specific outcome of stress depends on duration and severity of stressors (de Kloet et al., 2005; Joels, 2008). For example, acute stress increases total surface expression of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA receptor in PFC (Yuen et al., 2012) and increased associative learning (Joels, 2006; Shors et al., 1992), while chronic stress decreases total surface expression of NMDA receptor and impairs memory (Yuen et al., 2012). It has also been shown that chronic stress and the decrease of NR2A or NR2B-NMDAR impairs long-term potentiation (LTP) (von Engelhardt et al., 2008; Yuen et al., 2012). Furthermore, many reports suggest the close association of depressive behaviors with disrupted LTP in rodents (Gomez-Galan et al., 2013; Holderbach et al., 2007) and its reversal by increasing histaminergic signaling through H3R antagonism (Femenia et al., 2015). Thus, our results of chronic ciproxifan induced restoration of NR2A and NR2B expression in the hippocampus of CUS mice further corroborate the prevailing notion of increased HA signaling in the brain is essential for normal cognition.

5. Conclusion

Collectively, we conclude that chronic H3R antagonist treatment in CUS mice shows antidepressant like effect via modulating BDNF expression in PFC and hippocampus and resetting the overactive HPA-axis to the normal level. Furthermore, our in vitro experiments suggest that the increased HA due to the blockade of the auto-receptor function of H3R increases the expression of BDNF via H4R. Finally, these results provide important molecular insights underlying the beneficial effect of chronic H3R antagonism in depression-like conditions.

Author contributions

P.N.Y. designed the study, analyzed the data and prepared the draft of manuscript. A.K performed the experiments, analyzed the data and generated the all figures. S.D. generated Fig. 6 D and helped in behavioral experiments. CS helped in behavioral experiments, capturing and analyzing the microscopy data. DU helped in behavioral experiments. All authors editorial assistance in this manuscript.

Competing financial interests

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.11.007.

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