Neuroprotective effect of lurasidone via antagonist activities on histamine in a rat model of cranial nerve involvement

BAOMING HE, LIANG YU, SUPING LI, FEI XU, LILI YANG, SHUAI MA and YI GUO

Department of Neurology, Sichuan Academy of Medical Sciences, Sichuan People's Hospital, Chengdu, Sichuan 610072, P.R. China

Received March 25, 2016; Accepted March 11, 2017

DOI: 10.3892/mmr.2018.8595

Abstract. Cranial nerve involvement frequently involves neuron damage and often leads to psychiatric disorder caused by multiple inducements. Lurasidone is a novel antipsychotic agent approved for the treatment of cranial nerve involvement and a number of mental health conditions in several countries. In the present study, the neuroprotective effect of lurasidone by antagonist activities on histamine was investigated in a rat model of cranial nerve involvement. The antagonist activities of lurasidone on serotonin 5-HT_7, serotonin 5-HT_2A, serotonin 5-HT_1A and serotonin 5-HT_6 were analyzed, and the preclinical therapeutic effects of lurasidone were examined in a rat model of cranial nerve involvement. The safety, maximum tolerated dose (MTD) and preliminary antitumor activity of lurasidone were also assessed in the cranial nerve involvement model. The therapeutic dose of lurasidone was 0.32 mg once daily, administered continuously in 14-day cycles. The results of the present study found that the preclinical prescriptions induced positive behavioral responses following treatment with lurasidone. The MTD was identified as a once daily administration of 0.32 mg lurasidone. Long-term treatment with lurasidone for cranial nerve involvement was shown to improve the therapeutic effects and reduce anxiety in the experimental rats. In addition, treatment with lurasidone did not affect body weight. The expression of the language competence protein, Forkhead-BOX P2, was increased, and the levels of neuroprotective SxIP motif and microtubule end-binding protein were increased in the hippocampal cells of rats with cranial nerve involvement treated with lurasidone. Lurasidone therapy reinforced memory capability and decreased anxiety. Taken together, lurasidone treatment appeared to protect against language disturbances associated with negative and cognitive impairment in the rat model of cranial nerve involvement, providing a basis for its use in the clinical treatment of patients with cranial nerve involvement.

Correspondence to: Professor Liang Yu, Department of Neurology, Sichuan Academy of Medical Sciences, Sichuan People's Hospital, 32, First Ring Road West 2, Chengdu, Sichuan 610072, P.R. China
E-mail: yuliangprof@163.com

Key words: lurasidone, neuroprotection, cranial nerve involvement, antagonist

Introduction

Cranial nerve involvement frequently involves neuron damage, and often leads to psychiatric disorder caused by multiple inducements (1). Cranial nerve involvement affects cognitive impairments and mental health, and can lead to mental disability for patients worldwide (2). Patients with cranial nerve involvement account for >5% of the population, and is a common disabling mental disease with patients often suffering from complex psychiatric with cognitive, language, memory and behavior impairments (3,4). The key characteristics of cranial nerve involvement include neuron damage and cognitive impairment (5). However, the mechanism of multiple lower cranial nerve involvement associated with neuron damage and cognitive impairment remains to be fully elucidated. Therefore, understanding the signaling pathway between cranial nerve involvement and cognitive impairment is essential for the treatment of patients with cranial nerve involvement.

The role of histamine in cranial nerve involvement has received increasing attention in investigations. A previous study reported that the expression levels of histamine were upregulated in patients with cranial nerve involvement, formulating a stable protein complex target for histamine, which is important for maintaining the normal function of neurons, and critical for neuronal differentiation and brain development (6,7). The target for neuroprotective agents for neurocognitive repair and inhibition of neuron-function damage developed according to cognitive deficits across multiple domains in substantial intellectual impairment (8,9). In addition, although the theoretic mechanism of anti-histamine agents in cranial nerve involvement are well understood, treatment of this type of disease remains limited and lacks preclinical investigation (10-12). Therefore, investing the mechanism of anti-histamine in the treatment of cranial nerve involvement is important to better explain therapeutic effects according to observations.

Pharmaceutical studies have shown that anti-histamine drugs are efficient for the treatment of cranial nerve involvement (12,13). Lurasidone, is an azapirone derivative and a second-generation novel antipsychotic candidate, which was approved for the treatment of schizophrenia in the USA in

2010, and by the European Medicines Agency in 2014 (14,15). A previous report indicated that cranial nerve involvement was cured in some way following treatment with lurasidone in patients with schizophrenia (12). Additionally, lurasidone with lithium or valproate was identified as a therapeutic strategy for the treatment of bipolar I depression (15). The therapeutic mechanism underlying the effects of lurasidone involved decreased levels of serotonin 5-HT7, serotonin 5-HT_2A, serotonin 5-HT_1A and dopamine D_2 by antagonist activities (16).

In this present study, the therapeutic effects of lurasidone were investigated in a cranial nerve involvement rat model. On the basis of the aforementioned evidence, the present study examined the preclinical outcomes of lurasidone for cranial nerve involvement therapy. The data obtained suggested that lurasidone repaired neuron-function loss and improved anxiety, compared with a placebo. The results also suggested that cognitive ability was improved following treatment with lurasidone.

Materials and methods

Analysis of serotonin receptors and neuroprotective protein. Serotonin receptors and neuroprotective proteins in serum were analyzed using a commercialized ELISA kit in patients with cranial nerve involvement. A total of 180 patients and 124 healthy volunteers were recruited in Sichuan People's Hospital between April 2014 and December 2014. All patients were required to sign informed consent before the examinations. Serum was collected from 10 ml blood using centrifugation at 6,000 x g for 10 min at 4˚C. The ELISA assays were performed according to the manufacturer's protocols. The results were measured at 450 nm in an ELISA reader and finally converted to concentrations of serotonin 5-HT7, serotonin 5-HT_2A, serotonin 5-HT_1A, serotonin 5-HT_6, Forkhead-Box P2 (Foxp2), SxIP and microtubule end-binding (EB) protein.

Animal experiments. Rats (n=100) of a mutant intravenously mutated cranial nerve involvement Sprague-Dawley rat model (specific pathogen-free; 6-8 weeks old) were purchased from Slack Co., Ltd. (Shanghai, China). All rats were housed under controlled conditions (temperature, 23±1˚C, humidity, 55±5%) in a 12 h light/dark cycle with free access to food and water. The rats with cranial nerve involvement were randomly divided into two groups and injected intravenously with either lurasidone (0.32 mg) or placebo (PBS, 0.32 mg) as a control. The total treatment regime comprised a total of seven injections, once per day. All experimental procedures were performed according to the guidelines of Sichuan Academy of Medical Sciences, Sichuan People's Hospital (Sichuan, China). All experiments were approved by the Animal Care and Use Committee of Tianjin Medical (Tianjin, China).

Measurement of blood pressure, heart rate and blood glucose parameters. Blood levels in the rats with cranial nerve involvement were measured using a blood glucose gauge (OneTouch® VerioVue; Johnson & Johnson Medical (Shanghai) Ltd., Shanghai, China). The pressure was recorded prior to and following treatment with lurasidone or placebo. Heart rate and blood pressure parameters were measured every 2 days, as described in a previous report (17).

RNA isolation and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis. Total RNA was extracted from the hippocampal cells of the rats with cortical cranial nerve involvement following treatment with lurasidone or placebo using an RNAeasy Mini kit (Invitrogen; Thermo Fisher Scientific, Inc., Waltham, MA, USA). RNA (1 μg) was subjected to RT into cDNA using a reverse transcription kit (Invitrogen; Thermo Fisher Scientific, Inc.). The cDNA (10 ng) was used for qPCR analysis (Bio-Rad Laboratories, Inc., Hercules, CA, USA) with a SYBR-Green Master Mix system (Thermo Fisher Scientific, Inc.) and a total reaction volume of 25 μl (primers, 1 μl, cDNA, 2 μl, buffer, 2 μl, reverse transcriptase, 0.5 μl, SYBR, 0.5 μl and water, 19 μl). All forward and reverse primers were synthesized by Invitrogen; Thermo Fisher Scientific, Inc. (Foxp2, forward: 5'-AACAGA GACCACTGCAGGTGCC-3'; reverse: 5'-TCCCTGACG CTGAAGGCTGAG-3'; SxIP, 5'-TATGGTCTCTGCCTG TTGC-3', 5'-TGCTACTGCCCATTACAATTCC-3'; EB, forward: 5'-GGATTTGAATCACGTTTGTGTC-3', reverse: 5'-AACTTGCGCTCATCTTAGGC-3'; 5-HT7, forward: 5'-AATAAGGGTAAGCCAATTGTATGGA-3', reverse: 5'-TGGTGCAAAATCAACATTCC-3'; 5-HT6, forward: 5'-TATTACGAAGGCCAACCTAT-3', reverse: 5'-TTCTTC TTCAGGCAAATCAT-3'; 5-HT1A, forward: 5'-TCAAAA AGAAAGGAG-3', reverse: 5'-TCATCTGAGATAAGGGCT G-3'; 5-HT2A forward: 5'-TGTTTTAACGCCATTAGG TCA-3', reverse: 5'-TCCGAGCAACTGATAAGTCT-3' and β-actin, forward: 5'-CGGAGTCAACGGATTTGGTC-3', reverse: 5'-AGCCTTCTCCATGGTCGTGA-3').

Thermocycling conditions were as follows: Pre-denaturation at 95˚C for 90 sec, denaturation at 94.5˚C for 30 sec and annealing at 56˚C for 10 sec for 40 cycles. The alterations in relative mRNA expression levels were calculated using the $2^{-\Delta\Delta Cq}$ method (18), with the results expressed as the n-fold, compared with the control.

Western blot analysis. The hippocampal cells from the rats with cranial nerve involvement treated with lurasidone or placebo were homogenized in lysate buffer containing protease inhibitor and were centrifuged at 6,000 x g at 4˚C for 10 min. The supernatant was used to analyze proteins. For detection of proteins, the proteins were extracted using a protein extraction kit (Qiagen Sciences, Inc., Gaithersburg, MD, USA) according to the manufacturer's protocol. Protein concentration was measured using a BCA protein assay kit (Thermo Fisher Scientific, Inc.). Protein samples (20 μg/lane) were resolved by 15% SDS-PAGE and then transferred onto polyvinylidene fluoride membranes (Merck KGaA, Darmstadt, Germany) as previously described (19). For western blot analysis, primary antibodies: FoxP2 (ab16046), EB (ab157217), SxIP (ab45142), β-actin (ab8227) (all, 1:200; Abcam, Shanghai, China) were added for 12 h at 4˚C following blocking in 5% skimmed milk for 1 h at 37˚C. The sections were washed three times with PBS to remove primary antibodies and then incubated with HRP-labeled secondary goat anti-rabbit antibodies (ab150077; 1:2,000 dilution; Abcam) 24 h at 4˚C. The results were visualized using chemiluminescence detection system.

Immunofluorescence analysis. The therapeutic effects of lurasidone on neuronal repair were evaluated using

immunofluorescence staining of anti neuroprotection-associated proteins in the hippocampus of the experimental rats. Staining was performed on cerebral neurons of the hippocampus in randomly-selected animals from the lurasidone or placebo-treated groups. The immunofluorescence procedures were as previously reported and captured using a fluorescence microscope (FV3000; Olympus Corporation, Tokyo, Japan) at x40 magnification (20).

Experiments using the elevated plus maze trial and analysis of swimming duration. The anxiety of the rats was evaluated using an elevated plus maze trial based on the hypothesis that rat experience fear of open fields. The details of the elevated plus maze trial were as described in a previous study and the space was improved to a size of 80x15x60 cm (21). The rats with cranial nerve involvement were fixed at the center of the elevated plus maze, and these rats were positioned facing an open arm for a total of 5 min. The durations spent in the open and closed arms were recorded and calculated using the following formula: D2=(B - A)/(B + A). A represents the time spent in the open arm and the B represents the time spent in the closed arm. The anxious behavior was measured using the above formula and the path efficacy was calculated. The behavioral capacity of the rats with cranial nerve involvement was analyzed by swimming duration according to the method described in a previous study (22).

Efficacy and safety assessment. Assessments of efficacy and dose-limiting toxicity in the presence of lurasidone were performed in the present study. Safety assessments included the incidence rates (≥10%) of the most frequent treatment-emergent adverse events in a 30-day treatment period in the experimental and control groups. The efficacy and safety data included all rats in the cranial nerve involvement, therapeutic drug and control groups.

Statistical analysis. All data are presented as the mean ± standard error of the mean of triplicate experiments. All data were analyzed using SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA). Unpaired data was determined using Student's t test and comparisons of data between multiple groups were analyzed using one-way analysis of variance. Kaplan-Meier analysis was used to estimate the risk of relapse and re-treatment during the 368-day treatment period. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of the cranial nerve involvement rat model. Adult Sprague-Dawley (6-10 weeks old) rats with cranial nerve involvement were subjected to cerebral artery occlusion and reperfusion and examined in the designed experiments. The rats in the cranial nerve involvement model received lurasidone treatment or placebo treatment as a control. The preclinical parameters of cranial nerve involvement, including body temperatures, body weight, blood pressure, heart rate and blood glucose, were recorded prior to and following treatment. The characteristics of the rats and patients with cranial nerve involvement are summarized in Table I. The data indicated that the states of the rats with cranial nerve involvement, determined using the Positive and Negative Syndrome Scale (PANSS) were improved following lurasidone treatment, compared with the placebo. In addition, physiological parameters exhibited significant differences between the lurasidone and placebo groups. Of note, the mean blood pressure and heart rate during the experiment were significantly different between the lurasidone and placebo groups. In addition, the MTD was identified and the most common treatment-associated adverse events were hypertension, diarrhea, lethargy, rash, proteinuria and vomiting (Table II; ≥10%). A dose of 0.32 mg of lurasidone met criteria for further preclinical experiments in terms of the tolerability and therapeutic effects.

Detection of serum histamine and neuroprotective proteins in patients with cranial nerve involvement. A previous study indicated that histamine chemical compounds were

Table I. Characteristics of patients and rats with cranial nerve involvement.

Parameter	n	%
Total healthy volunteers	180	100
Men	85	47
Women	95	53
Total patients	124	100
Men	61	49
Women	63	51
Total rats with cranial nerve involvement	100	100
Male	50	50
Female	50	50
Positive and negative syndrome scale score	121.4±6.2	-
Body weight (g)	132±10.5	-
Blood glucose (mmol/l)	8.3±2.5	-
Blood pressure (mm Hg)	143±12	-
Heart rate	370±26	-
Drug therapy	80	100
Placebo	40	50
Lurasidone	40	50

Table II. Treatment-associated adverse effects of lurasidone with overall incidence ≥10%.

	Lurasidone (n=20 per group)			
Adverse effect	Total (n=60)	0.08-0.16 mg	0.25-0.32 mg	0.40 mg
Hypertension	12	3	4	5
Diarrhea	7	1	3	3
Proteinuria	9	2	3	4
Vomiting	10	2	3	5
Lethargy	8	2	3	3
Rash	9	2	3	4

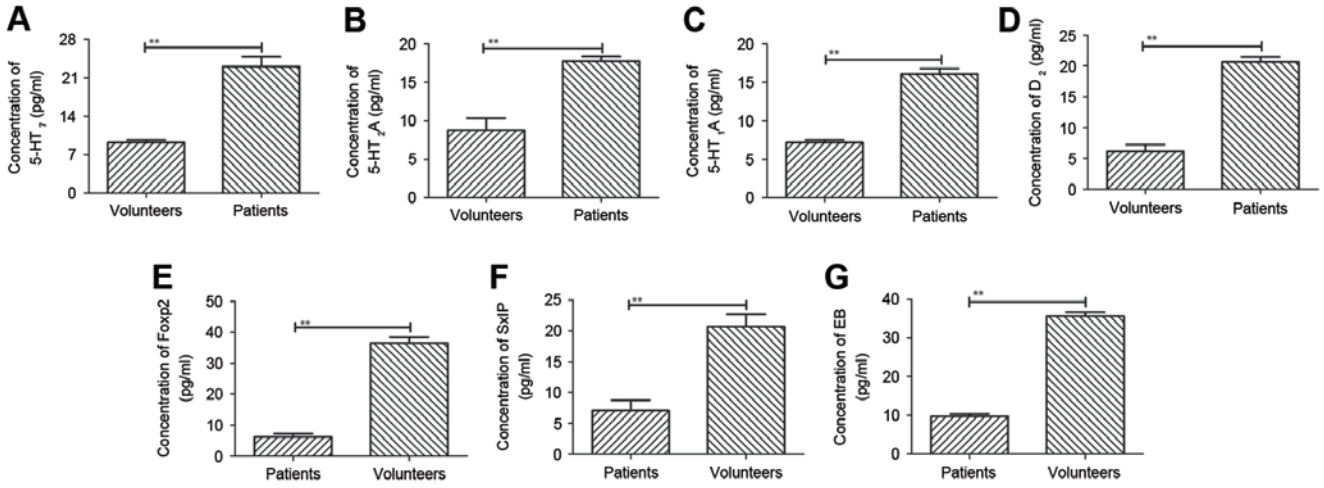

Figure 1. Expression of serotonin-media serotonergic neurons receptors and neuroprotective protein in patients with cranial nerve involvement and healthy volunteers. Differences in levels of (A) serotonin 5-HT_7, (B) serotonin 5-HT_2A, (C) serotonin 5-HT_1A and (D) serotonin 5-HT_6 between patients with cranial nerve involvement and healthy volunteers. Differences in levels of neuroprotective protein (E) Foxp2, (F) SxIP motif and (G) EB between patients with cranial nerve involvement and healthy volunteers. Data are presented as the mean ± standard of the mean. **P<0.01 (determined using one-way analysis of variance). Foxp2, Forkhead-Box P2; EB, microtubule end-binding protein.

upregulated in patients with cranial nerve involvement (23). In the present study, histamine chemical compounds, including serotonin 5-HT7, serotonin 5-HT_2A, serotonin 5-HT_1A, serotonin 5-HT_6, and the neuroprotective protein, Foxp2, SxIP motif and EB protein, were detected in sera of patients with schizophrenia. The concentrations of histamine chemical compound in the serum were elevated in patients with cranial nerve involvement, compared with healthy volunteers. The results, as shown in Fig. 1A-D, showed that plasma concentration levels of serotonin 5-HT_7, serotonin 5-HT_2A, serotonin 5-HT_1A and serotonin 5-HT_6 were downregulated, as determined using ELISA, compared with those of healthy volunteers. In addition, plasma concentration levels of three important neuroprotective protein, Foxp2, SxIP motifi and EB protein, were decreased in patients with cranial nerve involvement, compared with healthy volunteers (Fig. 1E-G). These results suggested that the expression levels of histamine were downregulated and may be associated with the expression of neuroprotective proteins.

Therapeutic effects of lurasidone in the cranial nerve involvement rat model. To investigate the beneficial preclinical outcomes of lurasidone, a rat model of cranial nerve involvement model was established. The results (Fig. 2A) indicated that the total PANSS score was significantly reduced in the rats with cranial nerve involvement treated with lurasidone compared with those treated with placebo. In addition, neuron impairment was analyzed on day 30 following lurasidone or placebo treatment. The results (Fig. 2B) showed that neuron impairment was significantly reduced in the hippocampus of lurasidone-treated mice. In addition, the risks of relapse and re-treatment in a 180-day observation period were analyzed following treatment with lurasidone, compared with the placebo. P-values were 0.00063 and 0.00048 for relapse rate and re-treatment, respectively (Fig. 2C and D). Furthermore, as shown in Fig. 2E and F, the lurasidone-treated mice had significantly higher rates of remission and reduced anxiety, compared with the placebo (P=0.0075 and P=0.0086, vs. placebo, respectively).

Neuroprotective effect of lurasidone in rats with cranial nerve involvement. The short-term and long-term effects of lurasidone were apparent in mice with cranial nerve involvement. In order to obtain further insight into the primary mechanism of lurasidone efficacy, the expression levels of Foxp2, SxIP and EB, and the distribution of neurons in the hippocampus were analyzed using RT-qPCR and immunohistochemcal analyses. The results (Fig. 3A) showed that the Foxp2 gene, associated with language competence, was increased in the hippocampus of the cranial nerve involvement rats following treatment with lurasidone (P=0.00044), compared with those in the placebo-treated group. In addition, the expression levels of neuroprotective SxIP motif and EB proteins were also upregulated following treatment with lurasidone, which led to neuroprotection and synaptic plasticity (Fig. 3B and C; P=0.0052 and P=0.0066, vs. placebo, respectively). As shown in Fig. 3D, the immunohistology revealed that neuron distributions were homogeneous in the hippocampus following treatment with lurasidone, compared with the placebo.

Antagonistic effect of lurasidone on histamine in rats with cranial nerve involvement. An important characteristic of cranial nerve involvement is anxiety. It was concluded that anxiety was in remission according to the experimental data. The behavior of rats with cranial nerve involvement was assessed using an improved water maze and recognition test. The results (Fig. 4A) indicated that the behavior of the rats with cranial nerve involvement improved following treatment with lurasidone, compared with the placebo (P=0.0059, vs. placebo). In addition, the data showed that lurasidone significantly improved cognitive impairment in rats with cranial nerve involvement (P=0.0059, vs. placebo; (Fig. 4B). Changes of histamine, including serotonin 5-HT_7, serotonin 5-HT_2A, serotonin 5-HT_1A, and serotonin 5-HT_6 in the serotonin systematic signaling pathway were also examined. The results (Fig. 4C) showed that the concentration levels of serotonin were downregulated in the cerebrospinal fluid of the lurasidone-treated rats, compared with the placebo-treated rats. The same observations

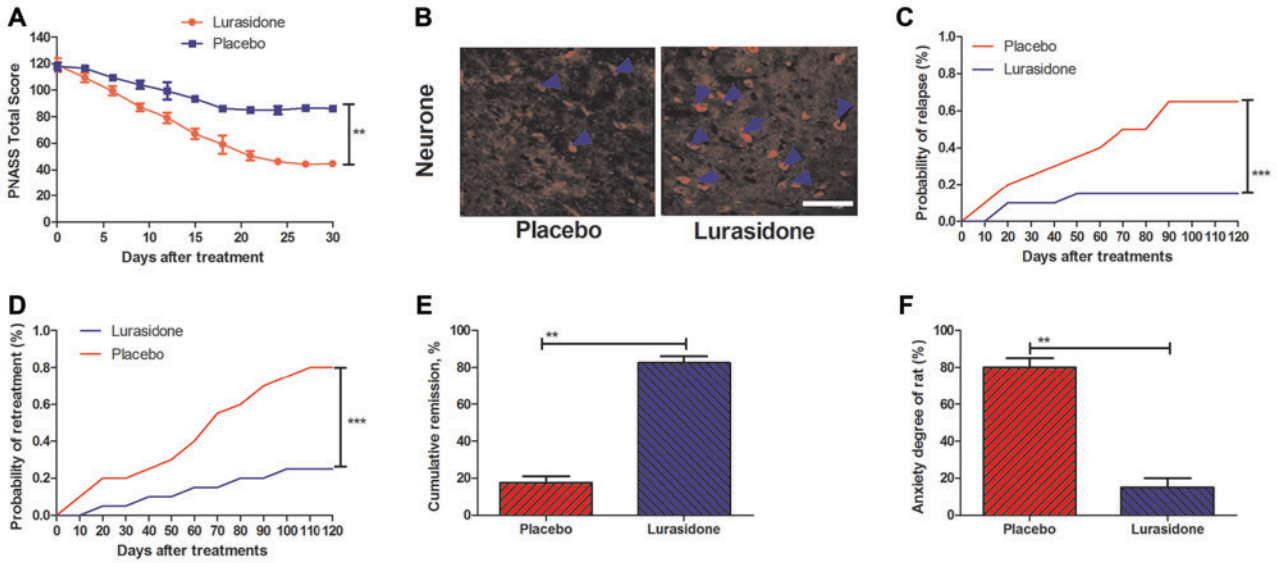

Figure 2. Short-term and long-term therapeutic effects of lurasidone on cranial nerve involvement in rats. (A) Total PANSS scores of rats with cranial nerve involvement treated with lurasidone or placebo in a 30-day short observation period. (B) Immunofluorescence staining showing numbers of neurons between the lurasidone- and placebo-treated rats with cranial nerve involvement. Scale bar=70 μm; arrows indicate neurons. (C) Kaplan-Meier estimated the probability of relapse during treatment with lurasidone or placebo. (D) Cumulative retreatment was evaluated by long-term observation. (E) Cumulative remission was evaluated by long-term observation between rats treated with lurasidone or placebo. (F) Anxiety in rats with cranial nerve involvement was evaluated using a plus-maze test by long-term observation between the lurasidone and placebo treatment groups. Student's t test and one way analysis of variance showed a statistically significant effect of treatment with cooperative therapy Data are presented as the mean ± standard error of the mean. **P<0.01 and ***P<0.001 between drug-treated and placebo groups. PANSS, Positive and Negative Syndrome Scale.

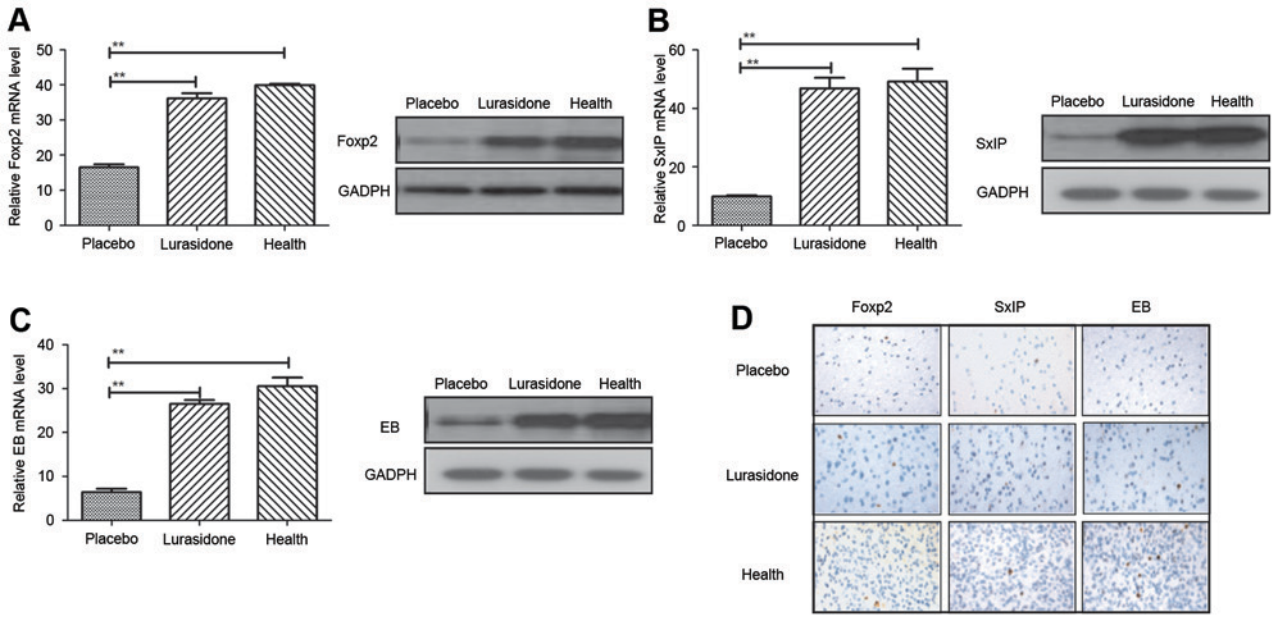

Figure 3. Therapeutic effects of lurasidone by increasing neuroprotective protein levels in the hippocampus. (A) Relative mRNA and protein expression of Foxp2 in the hippocampus. (B) Expression of SxIP motif in the hippocampus of rats with cranial nerve involvement following long-term treatment with lurasidone or placebo. (C) Expression of EB in the hippocampus of rats with cranial nerve involvement rat following long-term treatment with lurasidone or placebo. (D) Immunofluorescence staining analysis of the expression of Foxp2, SxIP motif and EB in the hippocampus of rats with cranial nerve involvement rat following long-term treatment with lurasidone or placebo. Magnification, x40. Data are presented as the mean ± standard error of the mean. **P<0.01 and ***P<0.001 between drug-treated and placebo groups.

were found in the hippocampus of cranial nerve involvement mice between the lurasidone and placebo groups (Fig. 4D). These data indicated that the serotonin systematic signaling pathway was inhibited by the antagonistic effect of lurasidone, which led to beneficial outcomes in behavior and cognitive improvements in the rats with cranial nerve involvement.

Discussion

Currently, although several factors have been reported to exhibit correlation with the initiation and development of cranial nerve involvement, the mechanism of interactions between cranial nerve involvement and affecting factors

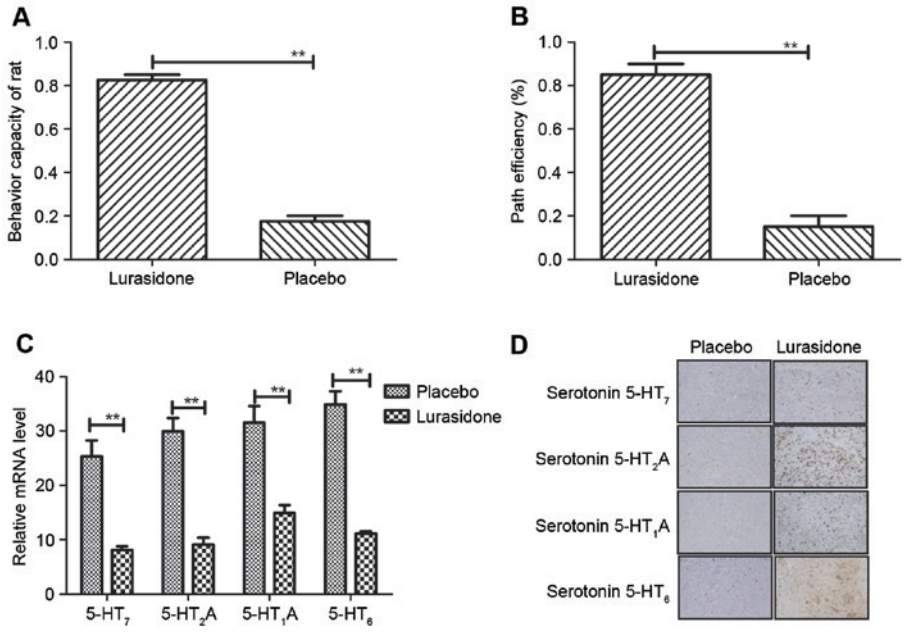

Figure 4. Efficacy of lurasidone by targeting antagonistic molecules. (A) Behavior capacity was analyzed by swimming following treatment with lurasidone or placebo. (B) Object recognition and short retention memory were assessed in rats with cranial nerve involvement following long-term treatment with lurasidone or placebo. Data are expressed as the mean ± standard error of the mean and total duration spent exploring all objects, determined by: Relative discrimination index=(duration in closed arms-duration in open arms)/(duration in closed arms + duration in open arms). (C) Differences in the mRNA expression levels of serotonin 5-HT_7, serotonin 5-HT_2A, serotonin 5-HT_1A and serotonin 5-HT_6 between the lurasidone and placebo-treated rats with cranial nerve involvement. (D) Expression levels of serotonin 5-HT_7, serotonin 5-HT_2A, serotonin 5-HT_1A and serotonin 5-HT_6, analyzed using immunofluorescence staining. **P<0.01 (determined using one-way analysis of variance).

remain to be fully elucidated (24). Several potentially neuroprotective agents function to upregulate gene transcription at the onset of brain ischemia, which may be an effective approach for limiting brain tissue damage (25). Studies on the mechanisms of cranial nerve involvement have shown that the serotonin systematic signaling pathway shows high correlation with the initiation, development, treatment and prognosis of cranial nerve involvement (26,27). In addition, an increasing number of studies have reported that the overexpression of histamine in the cerebrospinal fluid is a potential therapeutic target in patients with cranial nerve involvement and has been found be important in the pathogenesis of cranial nerve involvement (28-31).

Targeted therapy for cranial nerve involvement is a novel concept and the rationale for the trial in a mouse model of cranial nerve involvement, which was performed in a previous study (32). Serotonin is one of the most important predisposing and aggravating factors, which orchestrate the responses to neuron impairment and other exogenous insults (33). A previous study reported that serotonin was significantly correlated with neuron loss and continuation of non-motor symptoms in patients with Parkinson's disease treated with dopamine grafts (34). Serotonin has been shown to stimulate GnRH neuron excitability to exert biphasic actions through 5-HT1 and 5-HT2 receptors in the mouse indicated that 5-HT1 and 5-HT2 receptors were indicated as potential targets in the treatment of neuron impairment (31). Serotonergic neuron dysfunction in the hippocampal area is regulated by extracellular serotonin receptors, leading to hyperexcitability and discharge in the neurons (35). These findings suggest that the inhibition activity of the serotonin serotonergic neurons signaling pathway may benefit patients with cranial nerve involvement in clinical treatment.

A second antipsychotic agent, lurasidone, has been approved for the treatment of patients with schizophrenia and was identified as an adjunctive therapy with lithium or valproate for the treatment of bipolar I depression (15). In the present study, lurasidone was selected to investigate therapeutic efficacy in mice with cranial nerve involvement. Lurasidone is similar to the majority of antipsychotic drugs, in that it possesses an antagonist at serotonin 5-HT_7, serotonin 5-HT_2A, serotonin 5-HT_1A and serotonin 5-HT_6, respectively (12). However, reports on the clinical use of antipsychotic treatment for cranial nerve involvement are limited and primary mechanism of lurasidone as a long-term medicine remains to be fully elucidated.

In the present study, the efficacy of lurasidone in a rat model of cranial nerve involvement was evaluated. The antagonist of lurasidone for serotonin receptors was confirmed and demonstrated promising pharmacological function for the treatment of patients with cranial nerve involvement. The data demonstrated that 0.32 mg of lurasidone once a day was beneficial in the treatment of cranial nerve involvement. The body weight of the rats was minimally affected, and hypertension and heart rate parameters were low risk in terms of clinically meaningful alterations. Of note, cognitive competence was significantly improved following treatment with lurasidone, and lurasidone downregulated histamine receptors via the serotonin serotonergic neuron signaling pathway and increased the expression of neuroprotective proteins by impaired neurons. In conclusion, lurasidone showed efficacy in a rat model of cranial nerve involvement, and indicated that lurasidone may offer potential for application in the treatment of cranial nerve involvement.

References

1. Sakakibara Y, Mori M, Kuwabara S, Katayama K, Hattori T, Koga M and Yuki N: Unilateral cranial and phrenic nerve involvement in axonal Guillain-Barré syndrome. Muscle Nerve 25: 297-299, 2002.
2. Sahin E, Yilmaz A, Ersöz G, Uğuz M and Kaya A: Multiple cranial nerve involvement caused by Brucella melitensis. South Med J 102: 855-857, 2009.
3. Suzuki T: A further consideration on long-acting injectable versus oral antipsychotics in the treatment of schizophrenia: A narrative review and critical appraisal. Expert Opin Drug Deliv 13: 253-264, 2016.
4. Bortolato B, Miskowiak KW, Köhler CA, Vieta E and Carvalho AF: Cognitive dysfunction in bipolar disorder and schizophrenia: A systematic review of meta-analyses. Neuropsychiatr Dis Treat 11: 3111-3125, 2015.
5. Ushio M, Iwasaki S, Sugasawa K and Murofushi T: Superficial siderosis causing retrolabyrinthine involvement in both cochlear and vestibular branches of the eighth cranial nerve. Acta Otolaryngol 126: 997-1000, 2006.
6. Bahi A, Schwed JS, Walter M, Stark H and Sadek B: Anxiolytic and antidepressant-like activities of the novel and potent non-imidazole histamine H_3 receptor antagonist ST-1283. Drug Des Devel Ther 8: 627-637, 2014.
7. Borella L, Russell J, Rimele TJ, Grimes D, Failli A and Mir GN: Antisecretory and antiulcer activities of a potent new histamine H2-receptor antagonist with an intermediate duration of action. Arzneimittelforschung 38: 366-372, 1988.
8. Kent JS, Bolbecker AR, O'Donnell BF and Hetrick WP: Eyeblink conditioning in schizophrenia: A critical review. Front Psychiatry 6: 146, 2015.
9. McEvoy J and Citrome L: Brexpiprazole for the treatment of schizophrenia: A review of this novel serotonin-dopamine activity modulator. Clin Schizophr Relat Psychoses 9: 177-186, 2016.
10. Naito Y, Yoshikawa T, Matsuyama K, Yagi N, Nakamura Y, Nishimura S, Kaneko T, Yoshida N and Kondo M: Effect of the histamine H2-receptor antagonist (+/-)-(E)-1-[2-hydroxy-2-(4-hydroxyphenyl) ethyl]-3'-[2-[[[5-methylamino)methyl-2-furyl]methyl]thio] ethyl]-2'-(methylsulfonyl)guanidine on acute gastric mucosal injury in rats and its free-radical scavenging activities. Arzneimittelforschung 47: 845-848, 1997.
11. Ishikawa H, Ito H, Higaki M, Higaki M, Matsumoto Y, Kamimura T, Katsura Y, Tomishi T, Inoue Y, Takasugi H, *et al*: FR145715, a novel histamine H2 receptor antagonist, with specific anti-Helicobacter pylori activities. Eur J Pharmacol 378: 299-310, 1999.
12. Ishibashi T, Horisawa T, Tokuda K, Ishiyama T, Ogasa M, Tagashira R, Matsumoto K, Nishikawa H, Ueda Y, Toma S, *et al*: Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. J Pharmacol Exp Ther 334: 171-181, 2010.
13. Loebel A and Citrome L: Lurasidone: A novel antipsychotic agent for the treatment of schizophrenia and bipolar depression. BJPsych Bull 39: 237-241, 2015.
14. Citrome L: Lurasidone for schizophrenia: A review of the efficacy and safety profile for this newly approved second-generation antipsychotic. Int J Clin Pract 65: 189-210, 2011.
15. Loebel A, Cucchiaro J, Silva R, Kroger H, Sarma K, Xu J and Calabrese JR: Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: A randomized, double-blind, placebo-controlled study. Am J Psychiatry 171: 169-177, 2014.
16. Citrome L: Lurasidone in schizophrenia: New information about dosage and place in therapy. Adv Ther 29: 815-825, 2012.
17. Nunes PM, Wright AJ, Veltien A, van Asten JJ, Tack CJ, Jones JG and Heerschap A: Dietary lipids do not contribute to the higher hepatic triglyceride levels of fructose- compared to glucose-fed mice. FASEB J 28: 1988-1997, 2014.
18. Livak KJ and Schmittgen TD: Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods 25: 402-408, 2001.
19. Wai-Hoe L, Wing-Seng L, Ismail Z and Lay-Harn G: SDS-PAGE-Based quantitative assay for screening of kidney stone disease. Biol Proced Online 11: 145-160, 2009.
20. Dirani M, Nasreddine W, Abdulla F and Beydoun A: Seizure control and improvement of neurological dysfunction in Lafora disease with perampanel. Epilepsy Behav Case Rep 2: 164-166, 2014.
21. Vaisburd S, Shemer Z, Yeheskel A, Giladi E and Gozes I: Risperidone and NAP protect cognition and normalize gene expression in a schizophrenia mouse model. Sci Rep 5: 16300, 2015.
22. Berezova IV, Shishkina GT, Kalinina TS and Dygalo NN: Behavior in the forced-swimming test and expression of BDNF and Bcl-xl genes in the rat brain. Zh Vyssh Nerv Deiat Im I P Pavlova 61: 332-339, 2011 (In Russian).
23. Garcia-Calero E, Botella-Lopez A, Bahamonde O, Perez-Balaguer A and Martinez S: FoxP2 protein levels regulate cell morphology changes and migration patterns in the vertebrate developing telencephalon. Brain Struct Funct 221: 2905-2917, 2016.
24. Chebel S, Letaief L, Boughammoura-Bouatay A, Dachraoui F, Ouanes I, Ouanes-Besbes L, Abroug F and Frih-Ayed M: Multiple cranial nerve involvement: Consider the diagnosis of cephalic tetanus. A case report and review of the literature. Rev Neurol (Paris) 166: 948-950, 2010 (In French).
25. Mabray MC, Glastonbury CM, Mamlouk MD, Punch GE, Solomon DA and Cha S: Direct cranial nerve involvement by gliomas: Case series and review of the literature. AJNR Am J Neuroradiol 36: 1349-1354, 2015.
26. Mijajlovic M, Mirkovic M, Mihailovic-Vucinic V, Aleksic V and Covickovic-Sternic N: Neurosarcoidosis: Two case reports with multiple cranial nerve involvement and review of the literature. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 158: 662-667, 2014.
27. Galassi G, Albertini G, Valzania F and Barbieri A: Cranial nerve involvement as presenting sign of multifocal motor neuropathy. J Clin Neurosci 19: 1733-1735, 2012.
28. Watanabe Y, Someya T and Nawa H: Cytokine hypothesis of schizophrenia pathogenesis: Evidence from human studies and animal models. Psychiatry Clin Neurosci 64: 217-230, 2010.
29. de Witte L, Tomasik J, Schwarz E, Guest PC, Rahmoune H, Kahn RS and Bahn S: Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment. Schizophr Res 154: 23-29, 2014.
30. Debnath M and Chaudhuri TK: The role of HLA-G in cytokine homeostasis during early pregnancy complicated with maternal infections: A novel etiopathological approach to the neurodevelopmental understanding of schizophrenia. Med Hypotheses 66: 286-293, 2006.
31. Bhattarai JP, Roa J, Herbison AE and Han SK: Serotonin acts through 5-HT1 and 5-HT2 receptors to exert biphasic actions on GnRH neuron excitability in the mouse. Endocrinology 155: 513-524, 2014.
32. Girgis RR, Kumar SS and Brown AS: The cytokine model of schizophrenia: Emerging therapeutic strategies. Biol Psychiatry 75: 292-299, 2014.
33. Andrade R and Haj-Dahmane S: Serotonin neuron diversity in the dorsal raphe. ACS Chem Neurosci 4: 22-25, 2013.
34. Politis M, Wu K, Loane C, Quinn NP, Brooks DJ, Oertel WH, Björklund A, Lindvall O and Piccini P: Serotonin neuron loss and nonmotor symptoms continue in Parkinson's patients treated with dopamine grafts. Sci Transl Med 4: 128ra41, 2012.
35. Mlinar B, Montalbano A, Baccini G, Tatini F, Berlinguer Palmini R and Corradetti R: Nonexocytotic serotonin release tonically suppresses serotonergic neuron activity. J Gen Physiol 145: 225-251, 2015.