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Original Research

The therapeutic effect of quetiapine on cognitive impairment associated with 5-HT1A presynaptic receptor involved schizophrenia

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The cognitive impairment associated with schizophrenia is highly prevalent and affects the overall functioning of subjects. The stimulation of the serotonin 1A receptor is a primary characteristic of some atypical antipsychotic drugs. We measured the levels of cognitive impairment using the Morris water maze test and protein kinase A activity in hippocampal neurons on presynaptic and postsynaptic serotonin 1A receptors to investigate the effect of dizocilpine-induced cognitive impairment associated with atypical antipsychotic drugs in rats treated by quetiapine alone or combined with WAY100635/tandospirone. The results of the Morris water maze test presented evidence that quetiapine alone alleviated the cognitive impairment associated with atypical antipsychotic drugs induced by dizocilpine. However, quetiapine plus WAY100635 induced no improvement of cognitive impairment associated with atypical antipsychotic drugs. The results of protein kinase A assay suggested that neither quetiapine alone nor in combination with tandospirone, but not quetiapine plus WAY100635, raised protein kinase A activity in hippocampus neurons. The present study demonstrated the key role of presynaptic serotonin 1A receptors on the therapeutic effect of quetiapine on cognitive impairment associated with atypical antipsychotic drugs. Moreover, that protein kinase A activity in hippocampal cells is involved in the mechanism of quetiapine's effect on cognitive impairment associated with atypical antipsychotic drugs.

Keywords

Cognitive impairment; schizophrenia; quetiapine; 5-HT1A presynaptic receptors; 5-HT1A postsynaptic receptors; antipsychotic drugs

1. Introduction

Cognitive impairment associated with schizophrenia (CIAS) is highly prevalent and affects the overall functioning of subjects. The therapeutic effect of atypical antipsychotic drugs (AAPDs) on CIAS is better than that of typical antipsychotic drugs (APDs) (Harvey, 2006; Sharma, 1999). Stimulation of the serotonin 1A receptor (5-HT1A) is a primary characteristic of certain AAPDs (Kusumi et al., 2015). 5-HT1A is a metabotropic G protein-coupled receptor widely distributed in the frontal cortex, septum, amygdala, hippocampus and hypothalamus and is one of the main mediators of the action of 5-HT. Recently, a relationship between 5-HT1A receptors and cognitive function has been demonstrated, and 5-HT1A receptors have been proposed as targets for pharmacological treatment of cognitive impairment (Borg et al., 2006; Ogren et al., 2008). Quetiapine is a 5-HT1A partial agonist and features an impressive effect on the cognitive deficits of numerous psychiatric diseases (Ichikawa et al., 2002; Urben et al., 2012; Van den Eynde et al., 2009). 5-HT1A antagonists have been demonstrated to block the ameliorating effect of APDs on the cognitive impairments of schizophrenia (Nagai et al., 2009). Furthermore, AAPDs, combined with 5-HT1A agonists, which are usually used to treat anxiety and depression, have been demonstrated to exert a therapeutic effect on the cognitive impairments of schizophrenia (Ohno, 2010). Therefore, 5-HT1A activation may contribute to the beneficial effects of AAPDs on CIAS (Meltzer and Massey, 2011). However, a direct causal relationship between 5-HT1A and cognitive function and the underlying mechanisms has not been well established. Several studies questioned the role of 5-HT1A on the effect of AAPDs on CIAS, as no research data can rule out the possibility that 5-HT1A agonism improves the depression and negative symptoms associated schizophrenia, thus also contributing to the improvement of CIAS (Harvey, 2006; McGurk et al., 2000). To verify the role of 5-HT1A on the effect of AAPDs on CIAS, the neural mechanism of 5-HT1A should be clarified.

Notably, some studies report that 5-HT1A agonists attenuate cognitive deficits in certain neurological illnesses (Horiguchi et al., 2012; Olsen et al., 2012). However, several studies have suggested that cognitive deficits could be significantly alleviated by 5-HT1A antagonist and that 5-HT1A agonists contribute to cogni-

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tive deficits (Harder et al., 1996; Madjid et al., 2006). The reasons for these inconsistent results could be the complex mechanism of pre- and postsynaptic 5-HT1A receptors. 5-HT1A receptors are distributed in the soma and dendrites of 5-HTergic cells in the mammalian raphe nucleus and regulate 5-HT release (Assie et al., 2006). The postsynaptic 5-HT1A receptor is mainly distributed in non-5-HTergic cells in the mammalian hippocampus and regulates the release of glutamate, GABA and acetylcholine (Schechter et al., 2002). These 5-HT1A receptors also produce different or opposite effects. For example, the activation of presynaptic 5-HT1A receptors leads to reduced 5-HT release in the hippocampal dentate gyrus, which occurs when postsynaptic 5-HT1A receptors are blocked (Edagawa et al., 1998; Tachibana et al., 2004). Studies have noted that cognitive function is enhanced after the activation of the presynaptic 5-HT1A receptor, whereas it is significantly impaired after postsynaptic 5-HT1A receptor activation (Carli et al., 1998, 2001; Yasuno, 2004). Several 5-HT1A agonists or antagonists act on different 5-HT1A receptor subtypes under different conditions, thereby causing different biological responses (Ago et al., 2003; Carli et al., 1999; Millan et al., 1993). The 5-HT1A receptor agonist or inhibitor of the studies above possibly acted on either presynaptic or postsynaptic 5-HT1A receptors in different brain regions and led to the different or opposite reported results. Therefore, the effect of AAPDs on pre- and postsynaptic 5-HT1A receptors should be investigated.

Protein kinase A (PKA), a ubiquitous protein kinase in animals, is one of the most important signaling factors in the cyclic adenosine 3', 5' monophosphate (cAMP)-PKA pathway, which is a classical signaling pathway mediated by the 5-HT1A receptor that plays an important role in hippocampal-dependent memory formation. 5-HT1A activation reduces the production of cAMP, which in turn, inhibits PKA activity (Polter and Li, 2010; Zhu et al., 2004). PKA activity upregulates the transcription of memory-associated genes such as c-fos, c-jun, synapsin I, calmodulin-dependent protein kinase II and BDNF.

It is hypothesized that quetiapine improves cognitive function through its potentiation of PKA activity in hippocampal neurons, which is inhibited by 5-HT1A activation. 5-HT1A activation in hippocampal neurons is regulated by the presynaptic 5-HT1A receptor in the 5-HTergic cells of the raphe nucleus. Therefore, the aim of the present study is to investigate the effect of AAPDs on presynaptic 5-HT1A receptors by comparing the cognitive function and PKA activity in hippocampal neurons of dizocilpine-induced CIAS model rats treated with either quetiapine alone or quetiapine combined with a 5-HT1A presynaptic receptor agonist/antagonist.

2. Materials and methods

2.1 Animals

Adolescent, male Sprague-Dawley (SD) rats (age 28 days, weight 90 $\pm$ 5 g) were purchased from Sippr-BK Experimental Animal Ltd Co (Shanghai, China P.R.). They were group-housed (four per cage) in a controlled environment (23 $\pm$ 1 °C; 45--50% relative humidity; fixed 12/12h light/dark cycle) with food and water ad libitum for seven days before starting the experiment. Rats were randomly designed to control, Dizocilpine and three drug-treated groups (Que, Que & WAY, Que & Tan). There were 10 rats in each group. All procedures were approved by animal experiment ethics review of Fudan University Shanghai Medical College according to the National Institute of Health's Guide for the Use and Care of Laboratory Animals.

2.2 Drug administration

Dizocilpine, quetiapine, WAY100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-N-(2-pyridinyl) cyclohexane carboxamide, a potent and selective antagonist of the presynaptic 5-HT1A receptor) (Sato et al., 2007) and tandospirone (a partial 5-HT1A receptor agonist, and dose-dependent activator of both pre- and postsynaptic 5-HT1A receptor) (Huang et al., 2017; Kishimoto et al., 2000; Takada et al., 1996) were all purchased from Sigma-Aldrich Corporation (St. Louis, Mo., USA) and dissolved into polyethylene glycol 400 diluted with isotonic saline. Drugs were administered intraperitoneally or by lavage administration. All drugs were prepared daily before administration and administered between 9, and 10 am. Details of drug administration are given in Fig. 1. Drug doses used in this study were selected according to behavioral and neurochemical studies that showed the drugs had the intended effect (Nikiforuk, 2013; Snigdha et al., 2011; Uehara et al., 2014).

2.3 Morris water maze

Hippocampus-associated spatial memory was assessed using the Morris water maze (MWM) test 24 hours after the final administration of drugs, according to previously reported protocols (Beraki et al., 2009). The MWM is a circular pool (1.8 m diameter and 60 cm depth) nominally divided into four quadrants. An escape platform is located in the target quadrant, 1 cm below the water surface. Videotaping was conducted focusing on the full diameter of the pool. Trajectory and navigation parameters were recorded and analyzed by the ANY-maze video tracking system (Version 4.8; *Stoelting Co., Wood Dale, Il*). Rats were initially exposed to the maze eight times per day for four consecutive days. The probe trial was performed 24 hours after the last training session, the platform was removed from the maze, and the rats were placed in the pool for 60 s. The time spent in the target quadrant (TST) during the probe trial was evaluated to assess spatial memory retention of the escape platform's location, which was assumed to define the level of cognitive function. Swim speed (cm/s) was recorded and analyzed; this metric was assumed to quantify spontaneous locomotor activity and the emotional state of a rat.

2.4 PKA activity assay

48 hours after the WMW test, rats were deeply anesthetized with pentobarbital sodium 3% - 1 ml/kg body weight injected intraperitoneally. The rat's hippocampus was obtained. PKA activity was analyzed using PepTag® Non-Radioactive Protein Kinase Assays (Promega V5340). Briefly, 5 μl PepTag® PKA reaction buffer, 5 μl PepTag® A1 peptide, 5 μl PKA activator 5 $\times$ solution and 1 μl peptide protection solution were prepared in a 0.5 ml microcentrifuge tube. After incubation in a 30° C water bath for 2 minutes, 5 μl of 5 μM TAM-treated sample was added in a final volume of 25 μl with deionized water and incubated at 30 °C for 30 minutes. The reaction was stopped by heating to 95 °C for 10 minutes. The samples were separated on a 0.8% agarose gel at 100 V for 15 minutes. Phosphorylated peptide migrated toward the cathode (+), while nonphosphorylated peptide migrated

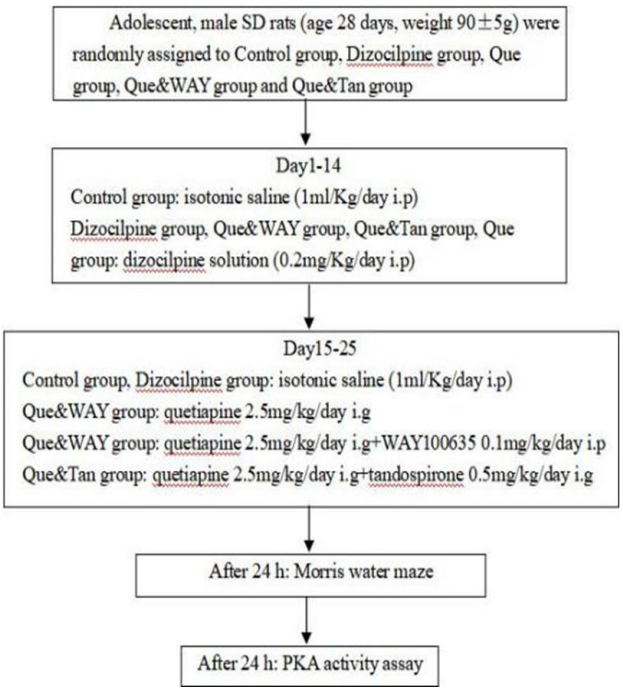

Figure 1. Experimental flow chart, CIAS model rats were made by dizocilpine; the rats were treated by quetiapine with or without tandozilpine/WAY100635; the cognitive function was measured using MWM test; PKA activity was analyzed using PepTag® Non-Radioactive Protein Kinase Assays.

toward the anode (-). PKA activity was quantified by densitometer using a wavelength of approximately 570 nm. The activity of PKA was expressed as the ratio of the optical density (OD) value of the phosphorylated peptide to the OD value of the nonphosphorylated peptide.

2.5 Statistical analysis

All data were analyzed using SPSS 19.0 (SPSS, Inc., Chicago, IL, USA). Data normality was assessed by the Kolmogorov--Smirnov test. Data showing normal distribution were summarized as mean ± standard deviation (SD). Unless otherwise specified, the data of the five groups were compared by one-way ANOVA with LSD (Least-Significant Difference) method as a *post hoc* analysis. Significance was assumed for $P < 0.05$.

3. Results

3.1 MWM test

Fig. 2a shows the five groups in the MWM test period. Rats in control, Quetiapine, and Que & Tan groups tended to swim near the platform. This indicates that they could better remember the position of the rest platform and tried to find it. An ANOVA analysis showed no significant difference in the average swimming speed between the five groups of rats (df = 4, F = 1.704, $P = 0.166$). This indicated that the spontaneous locomotor activity and emotional state of the rats in the five groups were similar (Fig. 2b). The ANOVA analysis showed a significant difference in TST between the five groups (df = 4, F = 4.581, $P = 0.003$) (Fig. 2c). A *post hoc* analysis showed that the TST of the Dizocilpine group was significantly shorter (mean difference = 3.82, $P = 0.016$) than that of controls. This indicated that rats exposed to sub-chronic and repeated Dizocilpine showed CIAS; the TST of the Quetiapine group was significantly higher than that of the Dizocilpine treated group (mean difference = 3.33, $P = 0.035$), which indicated that the CIAS induced by Dizocilpine was improved by Quetiapine. There was no significant difference in TST between the Dizocilpine and Que & WAY treated groups (mean difference = 1.08, $P = 0.483$). This means that CIAS was not improved by Quetiapine in the presence of WAY100365. The TST of the Que & Tan group was significantly longer than that of the Dizocilpine treated group (mean difference = 3.68, $P = 0.020$) but was not significantly different from that of the Quetiapine treated group (mean difference = 0.35, $P = 0.820$). This means that CIAS was improved by Quetiapine combined with Tandospirone, but that the effect of Quetiapine combined with Tandospirone was similar to Quetiapine alone.

3.2 PKA activity

As shown in Fig. 3, the ANOVA analysis of PKA activity in hippocampal neurons was significantly different for the five groups (df = 4, F = 1.704, $P = 0.166$). A *post hoc* analysis showed the level of PKA activity in the Dizocilpine treated group was not significantly different from that of the control group (mean difference = 0.35, $P = 0.494$). The PKA activity of the Quetiapine group was significantly higher than for the Dizocilpine group (mean difference = 2.68, $P = 3 \times 10^{-6}$). Moreover, the PKA activity of the Que & Tan group was significantly higher than that of the Quetiapine group (mean difference = 1.29, $P = 0.015$). However, there was no significant difference in PKA activity between the Que & WAY and Dizocilpine groups (mean difference = 0.05, $P = 0.915$).

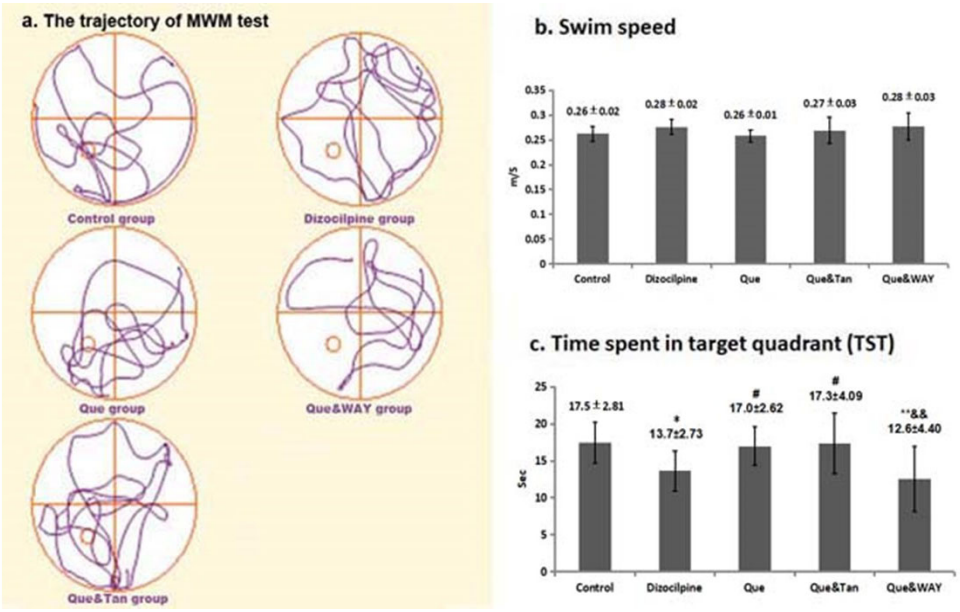

Figure 2. Comparative analysis of MWM test. (a) Trajectories of the rats in five groups during the probe trial. (b) ANOVA analysis result of swim speed during the probe trial. (c) ANOVA analysis result of TST during the probe trial. *: $P < 0.05$ *vs.* control group; **: $P < 0.01$ *vs.* control group; $^{\#}$: $P < 0.05$ *vs.* Dizocilpine group; $^{\#\#}$: $P < 0.01$ *vs.* Dizocilpine group; $^{\&}$: $P < 0.05$ *vs.* Quetiapine group; $^{\&\&}$: $P < 0.01$ *vs.* Quetiapine group.

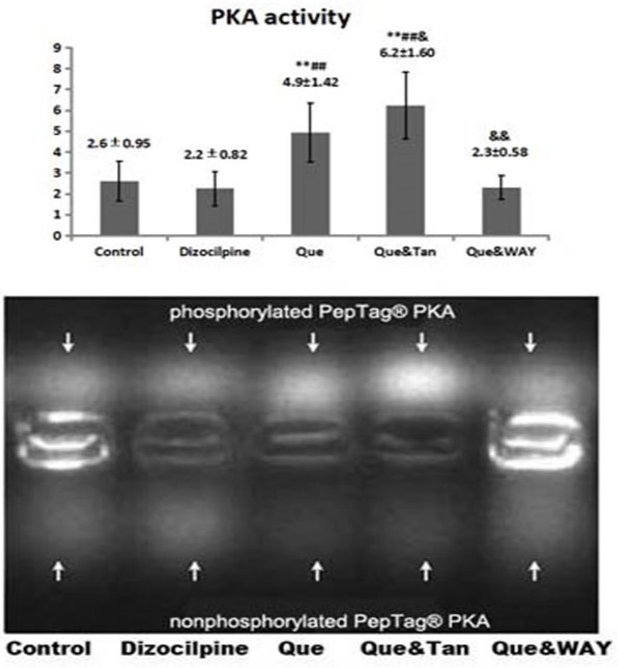

Figure 3. PKA activity in hippocampal neurons: The blots of PKA activity and ANOVA analysis of PKA activity in five groups. $^{*}P < 0.05$ *vs.* control group; $^{**}P < 0.01$ *vs.* control group; $^{\#}P < 0.05$ *vs.* Dizocilpine group; $^{\#\#}P < 0.01$ *vs.* Dizocilpine group; $^{\&}P < 0.05$ *vs.* Quetiapine group; $^{\&\&}P < 0.01$ *vs.* Quetiapine group.

4. Discussion

To clarify the effect of quetiapine on CIAS, in the present study CIAS model rats were induced with dizocilpine and then treated either with quetiapine alone or in combination with a 5-HT1A antagonist/agonist (WAY10065/tandospirone). The result of MWM testing indicated that a single dose of quetiapine alleviated dizocilpine-induced CIAS. However, treatment with a combination of quetiapine plus WAY100635 resulted in no improvement in the dizocilpine-induced CIAS. This finding means that quetiapine did not affect CIAS in the presence of WAY100635. This supports a role for 5-HT1A in the effect of quetiapine on CIAS. Notably, the present study revealed that co-administration

of the 5-HT1A agonist tandospirone resulted in no change in the therapeutic effect of quetiapine on CIAS. Some studies have shown that the addition of tandospirone enhanced the therapeutic effect of haloperidol on cognitive performance in schizophrenia (Sumiyoshi et al., 2001). However, several studies have suggested that tandospirone dose-dependently impaired memory through the stimulation of postsynaptic 5-HT1A receptors in hippocampal neurons, an effect that could be reversed by this 5-HT1A receptor antagonist (Mendelson et al., 1993). The previous studies reported that tandospirone regulates cognitive function in dizocilpine-treated rats (Bubenikova-Valesova et al., 2010). Tandospirone has also been found to activate presynaptic 5-HT1A receptors under certain conditions (Huang et al., 2017; Kishimoto et al., 2000; Takada et al., 1996). Therefore, it can be speculated that tandospirone has a dose-dependent effect on presynaptic/postsynaptic 5-HT1A receptors, which lead to the different effects on cognitive CIAS. Additionally, the co-administration of tandospirone only enhances the therapeutic effect on CIAS for typical antipsychotics (such as haloperidol) but does not affect 5-HT1A receptors in the case of AAPDs- (such as quetiapine).

To clarify the specific mechanism by which quetiapine improves CIAS through the 5-HT1A receptor, the present study investigated the level of PKA activity which plays an important role in the cognitive function of hippocampal cells. Previous studies have shown that dizocilpine decreases PKA activity in hippocampal cells (Al Rahim et al., 2009; Giordano et al., 2005). However, the present study revealed that PKA activity in the hippocampus of rats in the Dizocilpine group showed no difference to that of the control group. The main reason for this inconsistency is hypothesized to be that the rats in the Dizocilpine group were tested for PKA activity 10 days after the end of dizocilpine administration and by this time the dizocilpine has been completely metabolized. Thus, it's effect on PKA activity had ceased, although the dizocilpine induced CIAS still existed. It might be that dizocilpine has an immediate effect on PKA activity in the hippocampus neurons, which leads to long-lasting cognitive dysfunction. Although, it is necessary to clarify this putative effect of dizocilpine on hippocampal PKA levels in the future.

The present study also identified that the PKA activity in rats treated with quetiapine was significantly higher than that of the rats exposed only to dizocilpine. However, the PKA activity of rats treated with quetiapine plus WAY10036 was not significantly different from those exposed only to dizocilpine. These results suggest that quetiapine could increase PKA activity in the hippocampus that was blocked by the 5-HT1A antagonist. This demonstrates a key role for 5-HT1A in remediation of the effect of quetiapine on PKA activity. The studies mentioned above have suggested that either the activation of postsynaptic 5-HT1A receptors in hippocampus or the activation of presynaptic 5-HT1A receptors in the raphe nucleus leads to the opposite effect on PKA activity in hippocampus (Polter and Li, 2010; Zhu et al., 2004). It also suggests that quetiapine directly regulates presynaptic 5-HT1A receptors in the raphe nucleus, which in turn upregulates PKA activity in hippocampus. Additionally, it has been demonstrated that a low-dose of WAY100635 (0.1 mg/kg) primarily inhibits 5-HT1A presynaptic receptor activity, while a high dose (1 mg/kg) mainly inhibits 5-HT1A postsynaptic receptor activity (Sato et al., 2007). Therefore, in the present study, a low dose of WAY100635 (0.1 mg/kg) blocked the effect of quetiapine on presynaptic 5-HT1A receptors in raphe nucleus neurons. This further supports activation of presynaptic 5-HT1A receptors by quetiapine.

In the present study, tandospirone upregulated PKA activity in hippocampal cells in the presence of quetiapine, whereas, activation of either pres- or postsynaptic 5-HT1A receptors induced the opposite PKA activity in hippocampal neurons (Polter and Li, 2010; Zhu et al., 2004). The studies mentioned above support the fact that different doses of tandospirone activate either the presynaptic 5-HT1A receptors in hippocampus or the postsynaptic 5-HT1A receptors in the raphe nucleus. In the present study, tandospirone activated presynaptic 5-HT1A receptors in the raphe nucleus and upregulated the PKA activity in hippocampus. Additionally, the present study revealed that tandospirone induced no enhancement in the therapeutic effect of quetiapine on CIAS. This finding indicates that quetiapine plus 5-HT1A receptor agonist could upregulate the PKA activity in hippocampal cells but cannot enhance the therapeutic effect of quetiapine on CIAS. The reason for this might be that the PKA activity in hippocampal cells is not the only mechanism by which quetiapine influences CIAS.

The present study investigated the role of 5-HT1A receptors and PKA activity on the effect of quetiapine in CIAS and demonstrated a key role for presynaptic 5-HT1A receptors in the therapeutic effect of quetiapine on CIAS. It also identified that the PKA activity in hippocampal cells is involved in the mechanism of quetiapine's effects on CIAS. It should be noted that this study did not investigate the individual effects of tandospirone and WAY100635 on CIAS and PKA activity.

Author contributions

Hong Luo, Shenxun Shi, and Dai Han designed and managed the research data selection and analysis. Dai Han wrote the first draft of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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References

Ago, Y., Koyama, Y., Baba, A. and Matsuda, T. (2003) Regulation by 5-HT1A receptors of the in vivo release of 5-HT and DA in mouse frontal cortex. *Neuropharmacology* **45**, 1050-1056.

Al Rahim, M., Nakajima, A., Saigusa, D., Tetsu, N., Maruyama, Y., Shibuya, M., Yamakoshi, H., Tomioka, Y., Iwabuchi, Y., Ohizumi, Y. and Yamakuni, T. (2009) 4'-Demethylnobiletin, a bioactive metabolite of nobiletin enhancing PKA/ERK/CREB signaling, rescues learning impairment associated with NMDA receptor antagonism via stimulation of the ERK cascade. *Biochemistry* **48**, 7713-2771.

Assie, M. B., Lomenech, H., Ravailhe, V., Faucillon, V. and Newman-Tancredi, A. (2006) Rapid desensitization of somatodendritic 5-HT1A receptors by chronic administration of the high-efficacy 5-HT1A agonist, F13714: a microdialysis study in the rat. *British Journal of Pharmacology* **149**, 170-178.

Beraki, S., Diaz-Heijtz, R., Tai, F. and Ogren, S. O. (2009) Effects of repeated treatment of phencyclidine on cognition and gene expression in C57BL/6 mice. *International Journal of Neuropsychopharmacology* **12**, 243-255.

Borg, J., Andree, B., Lundberg, J., Halldin, C. and Farde, L. (2006) Search for correlations between serotonin 5-HT1A receptor expression and cognitive functions--a strategy in translational psychopharmacology. *Psychopharmacology (Berl)* **185**, 389-394.

Bubenikova-Valesova, V., Svoboda, J., Horacek, J. and Sumiyoshi, T. (2010) Effect of tandospirone, a serotonin-1A receptor partial agonist, on information processing and locomotion in dizocilpine-treated rats. *Psychopharmacology (Berl)* **212**, 267-276.

Carli, M., Balducci, C., Millan, M. J., Bonalumi, P. and Samanin, R. (1999) S 15535, a benzodioxopiperazine acting as presynaptic agonist and postsynaptic 5-HT1A receptor antagonist, prevents the impairment of spatial learning caused by intrahippocampal scopolamine. *British Journal of Pharmacology* **128**, 1207-1214.

Carli, M., Balducci, C. and Samanin, R. (2001) Stimulation of 5-HT(1A) receptors in the dorsal raphe ameliorates the impairment of spatial learning caused by intrahippocampal 7-chloro-kynurenic acid in naive and pretrained rats. *Psychopharmacology (Berl)* **158**, 39-47.

Carli, M., Bonalumi, P. and Samanin, R. (1998) Stimulation of 5-HT1A receptors in the dorsal raphe reverses the impairment of spatial learning caused by intrahippocampal scopolamine in rats. *European Journal of Neuroscience* **10**, 221-230.

Edagawa, Y., Saito, H. and Abe, K. (1998) 5-HT1A receptor-mediated inhibition of long-term potentiation in rat visual cortex. *European Journal of Pharmacology* **349**, 221-224.

Giordano, G., Sanchez-Perez, A. M., Montoliu, C., Berezney, R., Malyavantham, K., Costa, L. G., Calvete, J. J. and Felipo, V. (2005) Activation of NMDA receptors induces protein kinase A-mediated phosphorylation and degradation of matrin 3. Blocking these effects prevents NMDA-induced neuronal death. *Journal of Neurochemistry* **94**, 808-818.

Harder, J. A., Maclean, C. J., Alder, J. T., Francis, P. T. and Ridley, R. M. (1996) The 5-HT1A antagonist, WAY 100635, ameliorates the cognitive impairment induced by fornix transection in the marmoset. *Psychopharmacology (Berl)* **127**, 245-254.

Harvey, P. D. (2006) Cognitive and functional effects of atypical antipsychotic medications. *The Journal of Clinical Psychiatry* **67**, e13.

Horiguchi, M., Hannaway, K. E., Adelekun, A. E., Jayathilake, K. and Meltzer, H. Y. (2012) Prevention of the phencyclidine-induced impairment in novel object recognition in female rats by co-administration of lurasidone or tandospirone, a 5-HT(1A) partial agonist. *Neuropsychopharmacology* **37**, 2175-2183.

Huang, X., Yang, J., Yang, S., Cao, S., Qin, D., Zhou, Y., Li, X., Ye, Y. and Wu, J. (2017) Role of tandospirone, a 5-HT1A receptor partial agonist, in the treatment of central nervous system disorders and the underlying mechanisms. *Oncotarget* **8**, 102705-102720.

Ichikawa, J., Li, Z., Dai, J. and Meltzer, H. Y. (2002) Atypical antipsychotic drugs, quetiapine, iloperidone, and melperone, preferentially increase dopamine and acetylcholine release in rat medial prefrontal cortex: role of 5-HT1A receptor agonism. *Brain Research* **956**, 349-357.

Kishimoto, K., Koyama, S. and Akaike, N. (2000) Presynaptic modulation of synaptic gamma-aminobutyric acid transmission by tandospirone in rat basolateral amygdala. *European Journal of Pharmacology* **407**, 257-265.

Kusumi, I., Boku, S. and Takahashi, Y. (2015) Psychopharmacology of atypical antipsychotic drugs: From the receptor binding profile to neuroprotection and neurogenesis. *Psychiatry and Clinical Neurosciences* **69**, 243-258.

Madjid, N., Tottie, E. E., Luttgen, M., Meister, B., Sandin, J., Kuzmin, A., Stiedl, O. and Ogren, S. O. (2006) 5-Hydroxytryptamine 1A receptor blockade facilitates aversive learning in mice: interactions with cholinergic and glutamatergic mechanisms. *Journal of Pharmacology and Experimental Therapeutics* **316**, 581-591.

McGurk, S. R., Moriarty, P. J., Harvey, P. D., Parrella, M., White, L., Friedman, J. and Davis, K. L. (2000) Relationship of cognitive functioning, adaptive life skills, and negative symptom severity in poor-outcome geriatric schizophrenia patients. *Journal of Neuropsychiatry and Clinical Neurosciences* **12**, 257-264.

Meltzer, H. Y. and Massey, B. W. (2011) The role of serotonin receptors in the action of atypical antipsychotic drugs. *Current Opinion in Pharmacology* **11**, 59-67.

Mendelson, S. D., Quartermain, D., Francisco, T. and Shemer, A. (1993) 5-HT1A receptor agonists induce anterograde amnesia in mice through a postsynaptic mechanism. *European Journal of Pharmacology* **236**, 177-182.

Millan, M. J., Rivet, J. M., Canton, H., Lejeune, F., Gobert, A., Widdowson, P., Bervoets, K., Brocco, M. and Peglion, J. L. (1993) S 15535: a highly selective benzodioxopiperazine 5-HT1A receptor ligand which acts as an agonist and an antagonist at presynaptic and postsynaptic sites respectively. *European Journal of Pharmacology* **230**, 99-102.

Nagai, T., Murai, R., Matsui, K., Kamei, H., Noda, Y., Furukawa, H. and Nabeshima, T. (2009) Aripiprazole ameliorates phencyclidine-induced impairment of recognition memory through dopamine D1 and serotonin 5-HT1A receptors. *Psychopharmacology (Berl)* **202**, 315-328.

Nikiforuk, A. (2013) Quetiapine ameliorates stress-induced cognitive inflexibility in rats. *Neuropharmacology* **64**, 357-364.

Ogren, S. O., Eriksson, T. M., Elvander-Tottie, E., D'Addario, C., Ekstrom, J. C., Svenningsson, P., Meister, B., Kehr, J. and Stiedl, O. (2008) The role of 5-HT(1A) receptors in learning and memory. *Behavioural Brain Rresearch* **195**, 54-77.

Ohno, Y. (2010) New insight into the therapeutic role of 5-HT1A receptors in central nervous system disorders. *Central Nervous System Agents in Medicinal Chemistry* **10**, 148-157.

Olsen, A. S., Sozda, C. N., Cheng, J. P., Hoffman, A. N. and Kline, A. E. (2012) Traumatic brain injury-induced cognitive and histological deficits are attenuated by delayed and chronic treatment with the 5-HT1A-receptor agonist buspirone. *Journal of Neurotrauma* **29**, 1898-1907.

Polter, A. M. and Li, X. (2010) 5-HT1A receptor-regulated signal transduction pathways in brain. *Cellular Signalling* **22**, 1406-1412.

Sato, M., Ago, Y., Koda, K., Nakamura, S., Kawasaki, T., Baba, A. and Matsuda, T. (2007) Role of postsynaptic serotonin1A receptors in risperidone-induced increase in acetylcholine release in rat prefrontal cortex. *European Journal of Pharmacology* **559**, 155-160.

Schechter, L. E., Dawson, L. A. and Harder, J. A. (2002) The potential utility of 5-HT1A receptor antagonists in the treatment of cognitive dysfunction associated with Alzheimer s disease. *Current Pharmaceutical Design* **8**, 139-145.

Sharma, T. (1999) Cognitive effects of conventional and atypical antipsychotics in schizophrenia. *British Journal of Psychiatry* **38**, 44-51.

Snigdha, S., Idris, N., Grayson, B., Shahid, M. and Neill, J. C. (2011) Asenapine improves phencyclidine-induced object recognition deficits in the rat: evidence for engagement of a dopamine D1 receptor mechanism. *Psychopharmacology (Berl)* **214**, 843-853.

Sumiyoshi, T., Matsui, M., Nohara, S., Yamashita, I., Kurachi, M., Sumiyoshi, C., Jayathilake, K. and Meltzer, H. Y. (2001) Enhancement of cognitive performance in schizophrenia by addition of tandospirone to neuroleptic treatment. *American Journal of Psychiatry* **158**, 1722-1755.

Tachibana, K., Matsumoto, M., Togashi, H., Kojima, T., Morimoto, Y., Kemmotsu, O. and Yoshioka, M. (2004) Milnacipran, a serotonin and noradrenaline reuptake inhibitor, suppresses long-term potentiation in the rat hippocampal CA1 field via 5-HT1A receptors and alpha 1-adrenoceptors. *Neuroscience Letters* **357**, 91-94.

Takada, Y., Urano, T., Malyszko, J. and Takada, A. (1996) Changes in serotonergic measures in whole blood and various brain regions of rats administered with the 5-HT1A agonist tandospirone and/or exposed to electric foot-shock. *Brain Research Bulletin* **40**, 51-55.

Uehara, T., Matsuoka, T. and Sumiyoshi, T. (2014) Tandospirone, a 5-HT1A partial agonist, ameliorates aberrant lactate production in the prefrontal cortex of rats exposed to blockade of N-methy-D-aspartate receptors; Toward the therapeutics of cognitive impairment of schizophrenia. *Frontiers in Behavioral Neuroscience* **8**, 291.

Urben, S., Baumann, P., Barcellona, S., Hafil, M., Preuss, U., Peter-Favre, C., Clarke, S., Halfon, O. and Holzer, L. (2012) Cognitive efficacy of quetiapine in early-onset first-episode psychosis: a 12-week open label trial. *Psychiatric Quarterly* **83**, 311-324.

Van den Eynde, F., De Saedeleer, S., Naudts, K., Day, J., Vogels, C., van Heeringen, C. and Audenaert, K. (2009) Quetiapine treatment and improved cognitive functioning in borderline personality disorder. *Human Psychopharmacology* **24**, 646-649.

Yasuno, F. (2004) Hippocampal serotonin 1A receptor and memory function. *Seishin Shinkeigaku Zasshi* **106**, 1314-1322. (In Japanese)

Zhu, D. Y., Lau, L., Liu, S. H., Wei, J. S. and Lu, Y. M. (2004) Activation of cAMP-response-element-binding protein (CREB) after focal cerebral ischemia stimulates neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 9453-9457.