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Lack of rapid antidepressant effects of Kir4.1 channel inhibitors in a chronic social defeat stress model: Comparison with (*R*)-ketamine

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ABSTRACT

A recent study demonstrated a key role of astroglial potassium channel Kir4.1 in the lateral habenula in depression. We investigated whether Kir4.1 protein is altered in the brain regions from susceptible mice after a chronic social defeat stress (CSDS). Furthermore, we compared the rapid and sustained antidepressant actions of Kir4.1 inhibitors (quinacrine and sertraline) and (*R*)-ketamine, (*R*)-enantiomer of rapid-acting antidepressant (*R,S*)-ketamine, in a CSDS model. Western blot analysis of Kir4.1 protein in the brain regions (prefrontal cortex, nucleus accumbens, hippocampus) from CSDS susceptible mice and control mice (no CSDS) was performed. Quinacrine (15, or 30 mg/kg), sertraline (20 mg/kg), (*R*)-ketamine (10 mg/kg), or vehicle was administered intraperitoneally to CSDS susceptible mice. Subsequently, locomotion test, tail suspension test (TST), forced swimming test (FST) and 1% sucrose preference test (SPT) were performed. There were no changes of Kir4.1 protein in the all regions between two groups. (*R*)-ketamine showed rapid and long-lasting antidepressant actions in CSDS susceptible mice. In contrast, quinacrine and sertraline did not attenuate the increased immobility time of TST and FST in CSDS susceptible mice. Furthermore, quinacrine and sertraline did not improve decreased sucrose preference of SPT in CSDS susceptible mice. Unlike (*R*)-ketamine, quinacrine and sertraline did not show rapid and sustained antidepressant effects in a CSDS model. Therefore, it is unlikely that Kir4.1 channel inhibitors may have ketamine-like robust antidepressant actions although further study using selective and potent Kir4.1 channel inhibitors is needed.

1. Introduction

Multiple meta-analyses have demonstrated that the *N*-methyl-D-aspartate receptor (NMDAR) antagonist (*R,S*)-ketamine exhibits rapid antidepressant and anti-suicidal ideation effects in treatment-resistant patients with major depressive disorder or bipolar disorder (Kishimoto et al., 2016; Newport et al., 2015; Wilkinson et al., 2018; Xu et al., 2016). Off-label use of ketamine is increasing in the USA although the common adverse effects (e.g., psychotomimetic effects and dissociative effects) of (*R,S*)-ketamine are not resolved (Singh et al., 2017; Wilkinson et al., 2017). Thus, (*R,S*)-ketamine is the most attractive antidepressant in the treatment of severe depression (Abdallah et al., 2018; Chaki, 2017; Duman, 2018; Hashimoto, 2016a, 2016b; Monteggia and Zarate Jr, 2015; Zanos et al., 2018). However, the precise mechanisms underlying its antidepressant actions remain elusive.

(*R,S*)-ketamine (Ki = 0.53 μM for NMDAR) is a racemic mixture containing equal parts of (*R*)-ketamine (or arketamine) (Ki = 1.4 μM for NMDAR) and (*S*)-ketamine (or esketamine) (Ki = 0.30 μM for NMDAR) (Domino, 2010; Hashimoto, 2016a). It is reported that (*R*)-ketamine shows greater potency and longer-lasting antidepressant effects than (*S*)-ketamine in several animal models of depression (Fukumoto et al., 2017; Yang et al., 2015b, 2017a, 2017b, 2018; Zhang et al., 2014a; Zanos et al., 2016). Unlike (*S*)-ketamine, (*R*)-ketamine might not induce psychotomimetic side effects or exhibit abuse potential in rodents (Yang et al., 2015b, 2016a, 2016b). In addition, unlike (*R,S*)-ketamine and (*S*)-ketamine, (*R*)-ketamine did not cause the expression of heat shock protein HSP-70 (a marker for neuronal injury) in the rat retrosplenial cortex after a single administration (Tian et al., 2018). A positron emission tomography study showed a marked reduction of dopamine $D_{2/3}$ receptor binding in conscious monkey striatum after a single infusion of (*S*)-ketamine but not that of (*R*)-ketamine (Hashimoto et al., 2017), suggesting that (*S*)-ketamine-induced dopamine release might be associated with acute psychotomimetic and dissociative side effects

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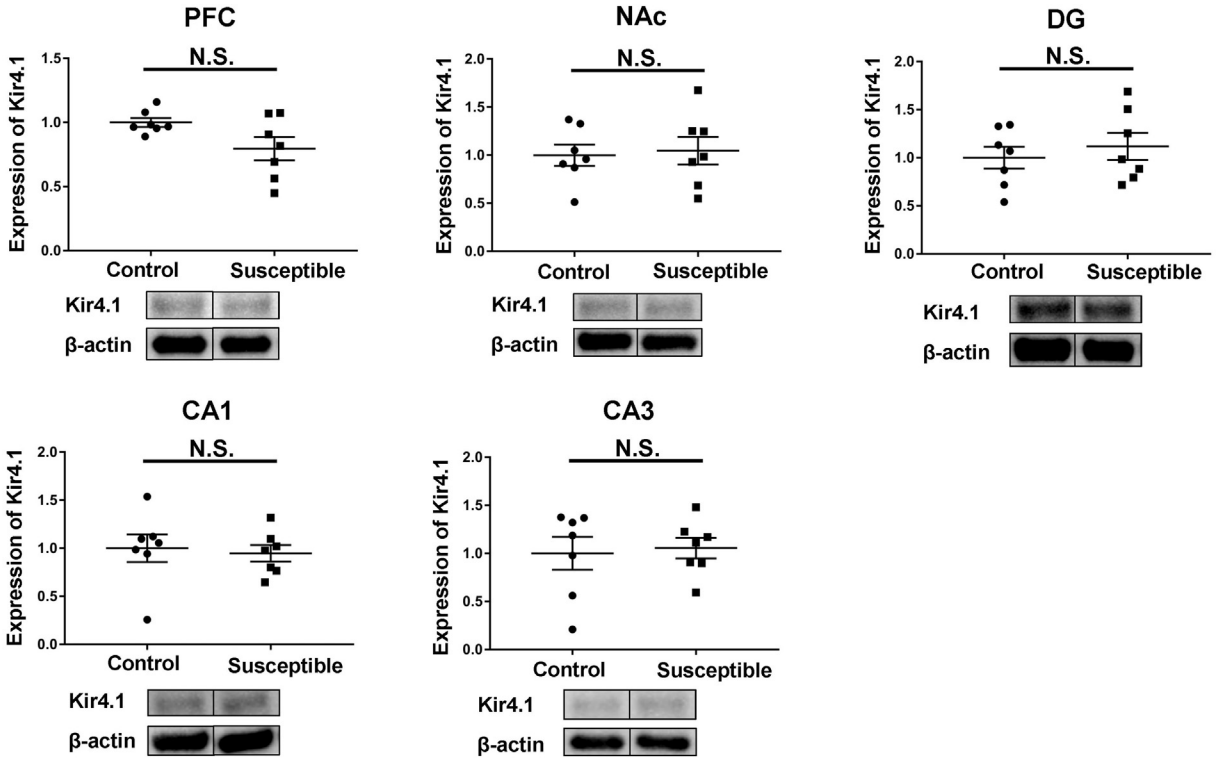

Fig. 1. Expression of Kir4.1 protein in the brain regions from CSDS susceptible mice and control mice.
Western bot analysis of Kir4.1 in the PFC, NAc, and DG, CA1, CA3 of hippocampus from CSDS susceptible mice and control (no CSDS) mice was performed. There were no changes of Kir4.1 protein in the all brain regions between two groups. The values represent the mean ± S.E.M. (n = 7). The band of gel was the representative of the group. N.S.: not significant.

in humans (Hashimoto et al., 2017). Therefore, (*R*)-ketamine could be a safer antidepressant in humans than (*R,S*)-ketamine and (*S*)-ketamine (Hashimoto, 2014, 2016a, 2016b, 2016c).

The inwardly rectifying potassium (Kir) channel Kir4.1 is responsible for astroglial potassium buffering (Butt and Kalsi, 2006; Ohno, 2018). Very recently, Cui et al. (2018) reported that astroglial Kir4.1 was upregulated in the laternal habenula (LHb) in rat models of depression, and that astrocyte-specific gain and loss function of Kir4.1 in the LHb bidirectionally regulated neuronal bursting and depression-like symptoms. This study strongly suggests that Kir4.1 in the LHb might have potential as a target for treating depression (Cui et al., 2018). However, the antidepressant effects of Kir4.1 inhibitors in a chronic social defeat stress (CSDS) model have not been reported.

Ohno et al. (2007) reported that the antidepressants such as selective serotonin reuptake inhibitors (SSRIs), including sertraline and fluoxetine, could inhibit Kir4.1 channel activity in a subunit-dependent manner. Interestingly, Kinboshi et al. (2017) reported that the antidepressants enhanced the brain-derived neurotrophic factor (BDNF) in astrocytes by inhibiting Kir4.1 channels. The order of the antidepressants for inhibiting Kir4.1-conducted potassium currents is as follows: sertraline > fluoxetine > imipramine > fluvoxamine (Kinboshi et al., 2017). Collectively, it is possible that astrocytic Kir4.1 channels may serve as novel therapeutic targets for depression (Ohno, 2018). In addition, quinacrine [6-chloro-9-(4-diethylamino-1-methylbutyl)amino-2-methoxyacridine dihydrochloride hydrate], a cationic amphiphilic drug, inhibits Kir4.1 channels in a concentration and voltage dependent manner (Marmolejo-Murillo et al., 2017).

The purpose of this study is to investigate whether Kir4.1 channels play a role in depression-like phenotype after CSDS. First, we examined whether Kir4.1 protein is altered in the brain regions of susceptible mice after CSDS. Second, we compared the rapid and long-lasting antidepressant effects of sertraline, quinacrine and (*R*)-ketamine in a CSDS model.

2. Methods and materials

2.1. Animals

Male adult C57BL/6 mice (n = 48), aged 8 weeks (body weight 20–25 g, Japan SLC, Inc., Hamamatsu, Japan) and male adult CD1 (ICR) mice (n = 40), aged 13–15 weeks (body weight > 40 g, Japan SLC, Inc., Hamamatsu, Japan) were used. Animals were housed under controlled temperatures and 12-hour light/dark cycles (lights on between 07:00–19:00 h), with ad libitum food (CE-2; CLEA Japan, Inc., Tokyo, Japan) and water. The protocol was approved by the Chiba University Institutional Animal Care and Use Committee (Permission number: 30-409). This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, USA. Animals were deeply anaesthetized with isoflurane before being killed by cervical dislocation. All efforts were made to minimize suffering.

2.2. Materials

(*R*)-ketamine hydrochloride was prepared by recrystallization of (*R,S*)-ketamine (Ketalar®, ketamine hydrochloride, Daiichi Sankyo Pharmaceutical Ltd., Tokyo, Japan) and D-(-)-tartaric acid, as described previously (Zhang et al., 2014a). The dose (10 mg/kg as hydrochloride) of (*R*)-ketamine dissolved in the physiological saline was used as previously reported (Yang et al., 2015b, 2017a, 2017b, 2018; Zhang et al., 2014a). The dose of quinacrine dihydrochloride (15 or 30 mg/kg: Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) was used as previously reported (Ahmad et al., 2014). Sertraline hydrochloride (20 mg/kg, Toronto Research Chemicals Inc., North York, ON, Canada) was dissolved in the physiological saline including 5% DMSO (Hirano et al., 2005; Ishima et al., 2009). Other reagents were purchased commercially.

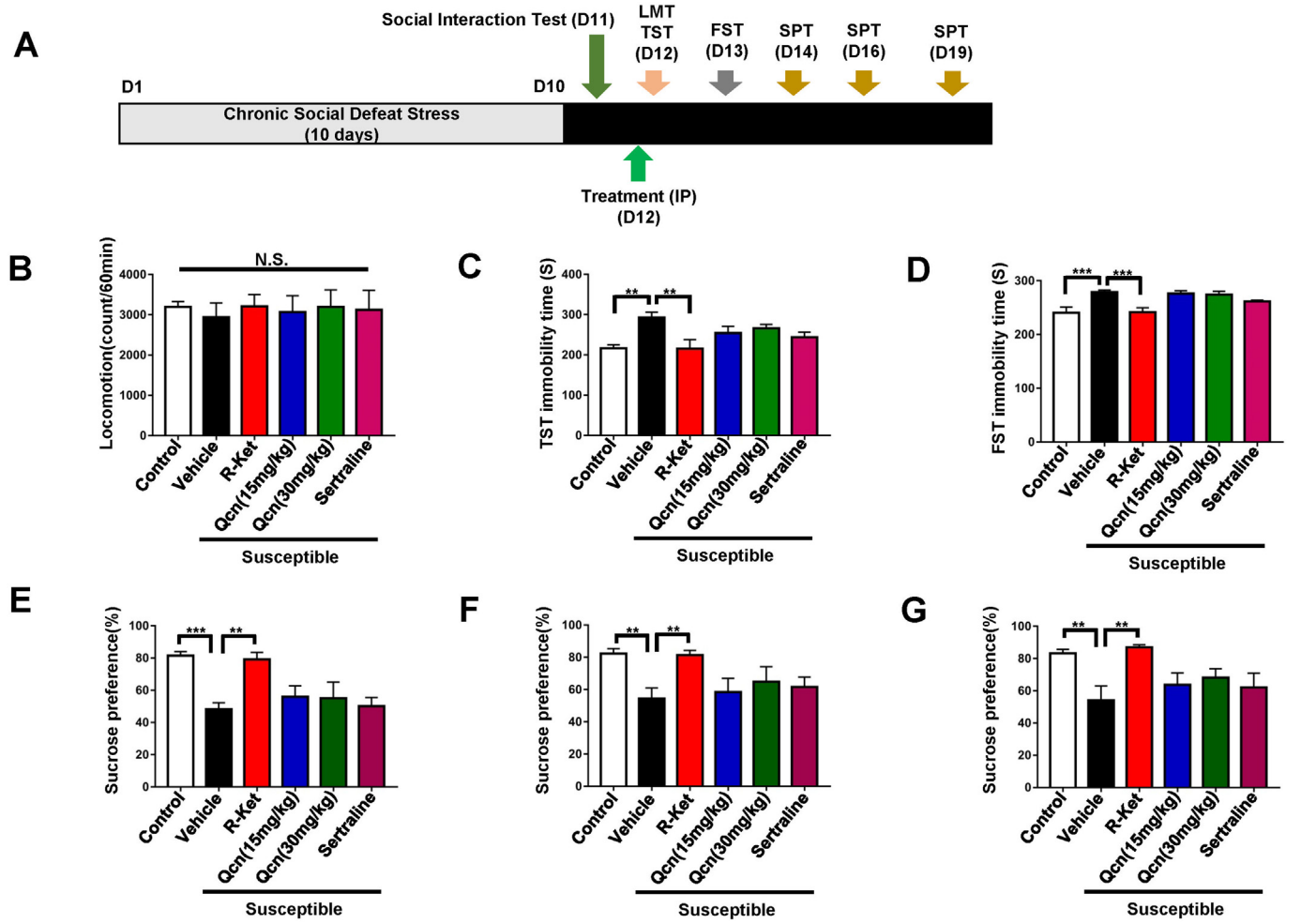

Fig. 2. Schedule of a CSDS model, treatment, and behavioral tests.
(A): CSDS was performed from day 1 to day 10, and the social interaction test (SIT) was performed on day 11. Vehicle (10 ml/kg), (*R*)-ketamine (10 mg/kg), quinacrine (15 or 30 mg/kg), or sertraline (20 mg/kg) was administered i.p. in the susceptible mice on day 12. LMT and TST were performed 2 and 4 h after a single injection, respectively. SPT was performed 2, 4 and 7 days after a single injection. (B): LMT. (day 12). (C): TST (day 12). (D): FST (day 13). (E): SPT (day 14). (F): SPT (day 16). (G): SPT (day 19). The values represent the mean ± S.E.M. (n = 8). **P < 0.01, ***P < 0.001 compared with vehicle-treated susceptible mice. N.S.: not significant. LMT: locomotion test. TST: tail suspension test. FST: forced swimming test. SPT: 1% sucrose preference test. R-ket: (*R*)-ketamine. Qcn: quinacrine.

2.3. Chronic social defeat stress (CSDS) model

The procedure of CSDS was performed as previously reported (Dong et al., 2017; Golden et al., 2011; Yang et al., 2015b, 2017a, 2017b, 2018; Zhang et al., 2015). The C57BL/6 mice were exposed to a different CD1 aggressor mouse for 10 min per day for consecutive 10 days. When the social defeat session ended, the resident CD1 mouse and the intruder mouse were housed in one half of the cage separated by a perforated Plexiglas divider to allow visual, olfactory, and auditory contact for the remainder of the 24-h period. At 24 h after the last session, all mice were housed individually. On day 11, a social interaction test (SIT) was performed to identify subgroups of mice that were susceptible and unsusceptible to social defeat stress. This was accomplished by placing mice in an interaction test box (42 × 42 cm) with an empty wire-mesh cage (10 × 4.5 cm) located at one end. The movement of the mice was tracked for 2.5 min, followed by 2.5 min in the presence of an unfamiliar aggressor confined in the wire-mesh cage. The duration of the subject's presence in the "interaction zone" (defined as the 8-cm-wide area surrounding the wiremesh cage) was recorded by a stopwatch. The interaction ratio was calculated as time spent in an interaction zone with an aggressor/time spent in an interaction zone without an aggressor. An interaction ratio of 1 was set as the cutoff: mice with scores < 1 were defined as "susceptible" to social defeat stress and those with scores ≥1 were defined as "resilient". Approximately 70–80% of mice were susceptible after CSDS. Susceptible mice were randomly divided in the subsequent experiments. Control C57BL/6 mice without CSDS were housed in the cage before the behavioral tests.

2.4. Western blot analysis

Brain regions of prefrontal cortex (PFC), nucleus accumbens (NAc), CA1, CA3, and dentate gyrus (DG) from hippocampus, were collected from control (no CSDS) mice and CSDS susceptible mice 9 days after social interaction test. The brain regions such as PFC, striatum, CA1, CA3 and DG of the hippocampus were dissected from brain on ice using a Leica microscope S9E (Leica Microsystems, Tokyo, Japan). Brain samples were stored at −80 °C until biochemical analyses. Tissue samples were homogenized in Laemmli lysis buffer, then centrifuged at 3000 ×*g* at 4 °C, for 10 min to obtain the supernatants. Protein concentrations were determined using a BCA method assay kit (Bio-Rad, Hercules, CA), then samples were incubated for 5 min at 95 °C, with an equal volume of 125 mM Tris/HCl, pH 6.8, 20% glycerol, 0.1% bromophenol blue, 10% β-mercaptoethanol and 4% sodium dodecyl sulfate. Proteins were separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis, on 10% mini-gels (Mini-PROTEAN®

TGX™ Precast Gel; Bio-Rad). Separated proteins were then transferred onto polyvinylidene difluoride membranes using a Trans Blot Mini Cell (Bio-Rad). For immunodetection, blots were blocked with 2% BSA in TBST (TBS + 0.1% Tween-20) for 1 h at room temperature (RT), then incubated with primary antibodies overnight, at 4 °C. The following primary antibodies were used: anti-potassium channel Kir4.1 (1:250, Cat#: MABN864, Merck, Tokyo, Japan) and β-actin (1:10,000, Sigma-Aldrich Co., Ltd., St Louis, MO, USA). The next day, blots were washed three times in TBST and incubated with horseradish peroxidase conjugated anti-rabbit or anti-mouse antibody (1:5000) for 1 h, at RT. After three washes in TBST, bands were detected using enhanced chemiluminescence (ECL), plus the Western Blotting Detection system (GE Healthcare Bioscience). Finally, blots were washed three times in TBST and incubated with a primary antibody directed against β-actin. Images were captured with a Fuji LAS3000-mini imaging system (Fujifilm, Tokyo, Japan), and immunoreactive bands were quantified.

2.5. Treatment and behavioral tests

The CSDS susceptible mice were divided to five groups. Subsequently, vehicle (10 ml/kg), (*R*)-ketamine (10 mg/kg), quinacrine (15, or 30 mg/kg), or sertraline (20 mg/kg) was administered intraperitoneally (i.p.) into mice (Fig. 2A). Behavioral tests, including locomotion test (LMT), tail suspension test (TST), forced swimming test (FST) and 1% sucrose preference test (SPT), were performed as reported previously (Dong et al., 2017; Yang et al., 2015b, 2017a, 2017b, 2018). LMT and TST were performed 2 and 4 h after a single injection, respectively. FST was performed 1 day after injection. SPT was performed 2, 4 and 7 days after a single injection.

2.5.1. Locomotion

The locomotor activity was measured by an animal movement analysis system SCANETMV-40 (MELQUEST Co., Ltd., Toyama, Japan). The mice were placed in experimental cages (length × width × height: 560 × 560 × 330 mm). The cumulative locomotor activity counts were recorded for 60 min. Cages were cleaned between testing session.

2.5.2. TST

A small piece of adhesive tape placed approximately 2 cm from the tip of the tail for mouse. A single hole was punched in the tape and mice were hung individually, on a hook. The immobility time was recorded for 10 min. Mice were considered immobile only when they hung passively and completely motionless.

2.5.3. FST

The FST was conducted using an automated forced-swim apparatus (SCANET MV-40; MELQUEST Co., Ltd., Toyama, Japan). Mice were placed individually in a cylinder (diameter: 23 cm; height: 31 cm) containing 15 cm of water maintained at a temperature of 23 °C ± 1 °C. The immobility time was calculated using the activity time as (total) – (active) time by the apparatus analysis software. The immobility time of each mouse was recorded for a period of 6 min.

2.5.4. SPT

Mice were exposed to water and 1% sucrose solution for 48 h, followed by 4 h of water and food deprivation and a 1-hour exposure to two identical bottles (water and 1% sucrose solution). The bottles containing water and sucrose were weighed before and at the end of this period. The sucrose preference was calculated as a percentage of sucrose solution consumption to the total liquid consumption.

2.6. Statistical analysis

The data show as the mean ± standard error of the mean (S.E.M.). Analysis was performed using PASW Statistics 20 (formerly SPSS Statistics; SPSS, Tokyo, Japan). The data of two groups were analyzed using Student *t*-test. The behavioral data were analyzed using the one-way ANOVA, followed by *post-hoc* Fisher's Least Significant Difference test. The P-values of < 0.05 were considered statistically significant.

3. Results

3.1. No changes of Kir4.1 protein in the brain regions from CSDS susceptible mice

We performed Western blot analysis of Kir4.1 protein in the PFC, hippocampus (CA1, CA3, DG), and NAc from CSDS susceptible mice and control (no CSDS) mice since Kir4.1 protein in the LHb was increased in the congenitally learned helpless (cLH) rats (Cui et al., 2018). There were no changes of Kir4.1 protein in the all brain regions between two groups (Fig. 1).

3.2. Effects of (R)-ketamine, quinacrine and sertraline in a CSDS model

Locomotion showed no difference ($F_{5,42} = 0.08$, $P = 0.995$) among the six groups (Fig. 2B). One-way ANOVA of TST data showed a statistical significance ($F_{5,42} = 4.064$, $P = 0.004$) among the six groups (Fig. 2C). *Post-hoc* tests showed that (*R*)-ketamine (10 mg/kg) significantly attenuated the increased immobility times of TST in susceptible mice after CSDS (Fig. 2C). However, quinacrine (15, or 30 mg/kg) or sertraline (20 mg/kg) did not attenuate the increased immobility times of TST in susceptible mice after CSDS (Fig. 2C). One-way ANOVA of FST data showed a statistical significance ($F_{5,42} = 6.755$, $P < 0.001$) among the six groups (Fig. 2D). *Post-hoc* tests showed that (*R*)-ketamine (10 mg/kg) significantly attenuated the increased immobility times of FST in susceptible mice after CSDS (Fig. 2D). However, quinacrine (15, or 30 mg/kg) or sertraline (20 mg/kg) did not attenuate the increased immobility times of FST in susceptible mice after CSDS (Fig. 2D). One-way ANOVA of SPT data showed statistical significances (2 days after a single injection: $F_{5,42} = 5.965$, $P < 0.001$, 4 days after a single injection: $F_{5,42} = 3.27$, $P = 0.014$, 7 days after a single injection: $F_{5,42} = 3.916$, $P = 0.005$) among the six groups (Fig. 2E–G). *Post-hoc* tests showed that sucrose preference of (*R*)-ketamine-treated group was significantly higher than vehicle-treated group. However, sucrose preference of quinacrine-treated group and sertraline-treated group was not different from vehicle-treated group (Fig. 2E–G).

These results suggest that, unlike (*R*)-ketamine, quinacrine and sertraline do not have rapid and sustained antidepressant effects in mice with depression-like phenotype in a CSDS model.

4. Discussion

In the present study, we found no changes of Kir4.1 channel in the brain regions from CSDS susceptible mice compared to control (no CSDS) mice. Furthermore, we found that a single dose of both quinacrine and sertraline did not show rapid and sustained antidepressant effects in a CSDS susceptible mice although a single dose of (*R*)-ketamine had rapid and long-lasting antidepressant effects in the same model. In this study, we used the two doses (15, or 30 mg/kg) of quinacrine in a CSDS model since the dose (15 and 30 mg/kg) of quinacrine was effective in rat lithium-pilocarpine model of status epilepticus (Ahmad et al., 2014). These data suggest that Kir4.1 channel may not play a major role in depression-like phenotype after CSDS, and that a single administration of Kir4.1 inhibitors does not have ketamine-like robust antidepressant actions in a CSDS model.

Interestingly, Cui et al. (2018) demonstrated higher expression of Kir4.1 channel in the LHb from cLH rats and LPS-treated rats although the other important brain regions (e.g., PFC, NAc, hippocampus) for depression were not examined. In this study, we did not find changes of Kir4.1 protein expression in these regions (PFC, NAc, hippocampus) from CSDS susceptible mice although alterations in the BDNF-TrkB signaling in these brain regions from rodents with depression-like

phenotype were shown (Dong et al., 2017; Ma et al., 2016; Shirayama et al., 2015; Yang et al., 2016a, 2016b; Yang et al., 2015a, 2015b; Zhang et al., 2014a, 2014b). Although the reasons underlying the discrepancy (our study vs. Cui et al., 2018) are currently unclear, the use of animals and models (CSDS susceptible mice for this study vs. cLH rats and lipopolysaccharide (LPS)-treated rats for Cui et al., 2018) may contribute to the discrepancy.

It is reported that Kir4.1 protein in the LHb from cLH rats and LPS-treated rats was higher than that in the control rats (Cui et al., 2018). Furthermore, astrocytic Kir4.1 overexpression increases neuronal bursts in the LHb and causes depression-like phenotypes, such as increased immobility time of FST and decreased sucrose preference of SPT (Cui et al., 2018). Interestingly, mice with AAV-GFAP::Kir4.1 infection in the LHb displayed severe depression-like phenotypes, including increased immobile duration and decreased latency to immobility in the FST, and decreased sucrose preference of SPT. Furthermore, infection with AAV-H1::Kir4.1-shRNA or AAV-GFAP::dnKir4.1 caused a pronounced reduction in the depression-like phenotypes of cLH rats (Cui et al., 2018). These data strongly suggests that blockade of Kir4.1 channel in the LHb can elicit the antidepressant effects (Cui et al., 2018). However, we did not find antidepressant effects of Kir4.1 channel inhibitors (quinacrine and sertraline) in a CSDS model. Although Kir4.1 channel in the LHb may play a role in depression-like phenotype, further detailed study on the role of Kir4.1 channel in the LHb in depression is needed.

In this study, we did not find antidepressant effects of a single dose of sertraline in a CSDS model, consistent with previous report using fluoxetine in a CSDS model (Ma et al., 2016). It is reported that social avoidance induced after CSDS can be reversed by chronic, but not acute, antidepressants (e.g., fluoxetine, imipramine) (Berton et al., 2006; Golden et al., 2011; Tsankova et al., 2006). Collectively, a single administration of antidepressants (e.g., sertraline, fluoxetine, imipramine) do not show antidepressant effects in a CSDS model although repeated administration of these antidepressants could show antidepressant effects in a CSDS model. Collectively, it is unlikely that the currently available antidepressants, including SSRIs (sertraline, fluoxetine), and Kir4.1 channel inhibitors may have ketamine-like rapid-acting and sustained antidepressant effects after a single dose. Nonetheless, it is of interest to study whether repeated administration of Kir4.1 channel inhibitors show antidepressant effects in a CSDS model.

This paper has two limitations. First, we did not examine the expression of Kir4.1 in the LHb in a CSDS model although the previous study showed higher levels of Kir4.1 in the LHb from cLH rats and LPS-treated rats (Cui et al., 2018). Second, we used non-selective Kir4.1 channel inhibitors (quinacrine, sertraline) to study their antidepressant effects in a CSDS model since the selective Kir4.1 channel inhibitors are currently not available. In order to assess antidepressant effects of Kir4.1 channel inhibitors, further detailed study using specific and potent Kir4.1 channel inhibitors is needed. Although quinacrine and sertraline did not show ketamine-like robust antidepressant effects in a CSDS model, the mechanisms by which (*R*)-ketamine results in rapid and long-lasting antidepressant effects remain to be determined.

In conclusion, this study suggests that, unlike (*R*)-ketamine, Kir4.1 channel inhibitors (quinacrine and sertraline) did not show the rapid and long-lasting antidepressant effects in a CSDS model. Therefore, it is unlikely that Kir4.1 channel inhibitors have ketamine-like robust antidepressant effects although further study using specific and potent inhibitors is needed.

Acknowledgements

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Conflict of interest

Dr. Hashimoto is an inventor on a filed patent application on “The use of (*R*)-ketamine in the treatment of psychiatric diseases” by Chiba University. Dr. Hashimoto has received research support from Dainippon-Sumitomo, Otsuka, and Taisho. Other authors declare no conflict of interest.

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