INTRODUCTION
Depression is one of the most common psychiatric disorders affecting nearly 20% of the population worldwide, and more than half of the suicides are accompanied by depression.\(^1\)\(^-\)\(^5\) Antidepressants such as selective serotonin reuptake inhibitors (5-hydroxytryptamine, 5-HT) and noradrenaline reuptake inhibitors are clinically prescribed drugs for the treatment of depression. However, it takes several weeks for these drugs to exert the antidepressant effects; moreover their remission rates are only approximately 40%.\(^3\)\(^,\)^\(^6\) Therefore, more studies are urgently needed to find a new, effective approach and to examine the pathophysiology of depression.

A number of studies have shown that a single subanesthetic dose of ketamine, a noncompetitive N-methyl-D-aspartate antagonist, produces rapid and sustained antidepressant effects in animal models\(^1\)^\(^-\)\(^9\) and in treatment-resistant patients with major depressive disorder and bipolar disorder.\(^1\)^\(^0\)\(^-\)\(^1\)\(^3\) Several molecular mechanisms, neural circuits and signal transduction pathways have been involved in the mechanism of ketamine’s antidepressant effect; however, the precise mechanisms underlying its antidepressant effect remain largely to be determined.\(^1\)^\(^4\)\^-\)\(^1\)^\(^9\)

The protein p11 (also known as S100A10), a member of the S100 EF-hand protein family, is widely expressed in several brain regions that are implicated in the pathophysiology of depression, including the hippocampus and frontal cortex.\(^2\)^\(^0\)\^-\)\(^2\)^\(^2\) Accumulating evidence suggests a key role of p11 in the pathophysiology of depression. The levels of mRNA and protein of p11 are down-regulated in the hippocampus of rodents with depression-like phenotype and the peripheral blood mononuclear cells of depressed patients.\(^2\)^\(^3\)\^-\)\(^2\)^\(^4\) Furthermore, decreased p11 mRNA levels are also observed in the hippocampus of suicide victims.\(^2\)^\(^5\) Interestingly, the overexpression of p11 can rescue the depression-like phenotype in p11 knockout mice, and selective serotonin reuptake inhibitors or tricyclic antidepressants promote the expression of p11 in the frontal cortex and hippocampus of rodents.\(^2\)^\(^3\)\^-\)\(^2\)^\(^6\)

Clinical and preclinical studies report that ketamine can increase brain-derived neurotrophic factor (BDNF), and that BDNF and its receptor tropomyosin-related kinase B (TrkB) may have a role in the antidepressant-like activity of ketamine.\(^9\)^\(^,\)^\(^2\)^\(^7\)\^-\)\(^2\)^\(^9\) Interestingly, it is reported that BDNF can regulate the expression of p11 in vivo and in vitro.\(^3\)^\(^0\) However, it remains unknown whether p11 participates in the antidepressant-like activity of ketamine. Therefore, the purpose of this study was to investigate the role of p11 in the rapid and sustained antidepressant-like activity of ketamine in chronic unpredictable mild stress (CUMS) rats.

MATERIALS AND METHODS
Animals
Adult male Sprague Dawley rats (250–300 g) purchased from comparative medicine of Jinling Hospital were housed at 21 °C and maintained on 12-h
light/dark cycle (light on at 0700). Food and water was obtained ad libitum. This study was approved by the Ethics Committee of Jinling Hospital, Nanjing, China, and performed in accordance with the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health, USA.

Design and drug interventions
A total of 96 rats were divided into seven groups: control group (n = 24), CUMS+saline group (n = 16), CUMS+ketamine group (n = 16), CUMS+ketamine+ANA-12 (a selective TrkB antagonist)31 group (n = 16), LV-eGFP (lentivirus with enhanced green fluorescent protein) group (n = 8), LV-p11-eGFP+saline group (n = 8), LV-p11-eGFP+ketamine (n = 8).

Ketamine hydrochloride (Gustan Pharmaceutical Company, Fujian, China) at 10 mg kg$^{-1}$ was intraperitoneally administered 0.5 h or 72 h before the behavioral tests. ANA-12 (0.5 mg kg$^{-1}$, Sigma Chemical, St Louis, MO, USA) was intraperitoneally administered with ketamine (10 mg kg$^{-1}$).

CUMS protocol
The depression model was set up by the CUMS as described previously with a slight modification.32 The rats in the CUMS groups were exposed to 10 different stressors for 20 days (two stressors per day), namely, 24 h food deprivation, 24 h water deprivation, 24 h 45° tilted cages, damp bedding, lights on overnight, lights off daytime, 5-min rotation on a shaker, placement in a 4 °C environment, isolation and crowding. At day 21, the rats were forced to swim for 15 min in a cylindrical tank (diameter 30 cm, height 75 cm) filled with 22 °C water (depth 40 cm).

Lentivirus production, screening and stereotaxic injection
To silence p11 in the hippocampus, three lentiviruses (LVs) targeting different sequences of p11 were constructed (Gene Chem, Shanghai, China). The p11 LV-A (5′-TCCCAAATGGAGCATGCCA-3′) and LV-C (5′-GTACACATGAAGCAGAAGA-3′) were screened by western blotting to determine which LV can maximally silence the expression of p11 in neural culture cells.

Primary hippocampal neurons were isolated from 18-day timed pregnant Sprague Dawley rats, as previously described.33 Neurons were cultured for 7 days in vitro in neurobasal B27 (1:50 dilution; Invitrogen, Shanghai, China) supplemented medium (Gibco, Invitrogen), cultured for 7 days 

Statistical analysis
Data are expressed as mean ± s.e.m. and were analyzed by Statistical Package for Social Sciences (SPSS version 17.0, SPSS IBM, Chicago, IL, USA). Statistical significance among groups was assessed by one-way analysis of variance (ANOVA), followed by post hoc Bonferroni tests. P < 0.05 was considered statistically significant.

RESULTS
Levels of hippocampal p11, BDNF, proBDNF, TrkB and p-TrkB in the rapid antidepressant-like activity of ketamine
To test the rapid antidepressant-like activity of ketamine, open-field test and FST were performed at 0.5 h after ketamine or saline administration (Figure 1a). No significant difference (F(3,28) = 0.297, P = 0.82) was found in the total distance among the four groups (Figure 1b). One-way ANOVA of FST data revealed significant differences among the four groups (F(3,28) = 7.921, P < 0.01). In the FST, the immobility time of the saline-treated group of CUMS rats was significantly (P < 0.01) higher than that of the control group (Figure 1c). The immobility time of the ketamine-treated group of CUMS rats was significantly (P < 0.01) lower than that of the saline-treated group of CUMS rats (Figure 1c). Furthermore, co-administration of ANA-12 significantly (P < 0.05) blocked the antidepressant effect of ketamine in CUMS rats (Figure 1c).

One-way ANOVA of p11 data revealed significant differences among the four groups (F(3,8) = 50.673, P < 0.001). Levels of p11 in the hippocampus of CUMS rats were significantly (P < 0.001) lower than those of the control rats (Figure 1d). Ketamine or a
Combination of ketamine and ANA-12 did not alter the reduced levels of p11 in the hippocampus of CUMS rats (Figure 1d). One-way ANOVA of BDNF data revealed significant differences $(F(3,8) = 43.574, P < 0.001)$ among the four groups. Levels of BDNF in the hippocampus of CUMS rats were significantly $(P < 0.001)$ lower than those of the control rats (Figure 1e). Ketamine or a combination of ketamine and ANA-12 significantly $(P < 0.01)$ increased the levels of BDNF in the hippocampus to control levels (Figure 1e).

One-way ANOVA of proBDNF data revealed no significant difference among the four groups $(F(3,28) = 0.752, P = 0.55)$ (Figure 1f). The ratio of p-TrkB to total TrkB data revealed significant difference among the four groups $(F(3,8) = 31.803, P < 0.01)$. The ratio of p-TrkB to total TrkB was significantly $(P < 0.001)$ lower in the CUMS rats than in the controls (Figure 1g). Ketamine significantly $(P < 0.05)$ increased the ratio of p-TrkB to total TrkB in the hippocampus of CUMS rats, which could be blocked by the co-administration of ANA-12 (Figure 1g).
Levels of hippocampal p11, BDNF, proBDNF, and p-TrkB/TrkB in the sustained antidepressant-like activity of ketamine

To test the sustained antidepressant-like activity of ketamine, open-field test and FST were performed at 72 h and SPT during a 3-day period after administration of saline, ketamine or a combination of ketamine and ANA-12 (Figure 2a). The total distance among the groups had no significant difference (F(3,28) = 0.980, P = 0.42; Figure 2b). One-way ANOVA of FST data revealed significant differences among the four groups (F(3,28) = 9.293, P < 0.001). The immobility time of the saline-treated group of CUMS rats was significantly (P < 0.05) higher than that of the ketamine-treated group of CUMS rats (Figure 2c). Furthermore, co-administration of ANA-12 significantly (P < 0.05) blocked the anti-anhedonia effect of ketamine in CUMS rats (Figure 2d). In contrast, in the SPT, there was no significant difference in the total volume consumed among the groups (F(3,28) = 1.405, P = 0.27; Figure 2e).

One-way ANOVA of p11 data revealed significant differences among the four groups (F(3,28) = 7.992, P < 0.01). Levels of p11 in the hippocampus of CUMS rats were significantly lower than those of the control rats (Figure 2f). Ketamine significantly attenuated the reduced levels of p11 in the hippocampus of CUMS rats compared with the saline-treated group of CUMS rats (Figure 2f). Interestingly, co-administration of ANA-12 significantly blocked the effect of ketamine on p11 expression in the hippocampus (Figure 2f).

One-way ANOVA of BDNF data revealed significant differences among the four groups (F(3,28) = 8.875, P < 0.01). Levels of BDNF in the hippocampus of CUMS rats were significantly lower than those of the control rats (Figure 2g). Ketamine or a combination of ketamine and ANA-12 significantly (P < 0.05) increased levels of BDNF in the hippocampus of CUMS rats compared with the saline-treated group of CUMS rats (Figure 2g).
One-way ANOVA of proBDNF data revealed no significant difference \( F(3,8) = 1.605, P = 0.263 \) among the four groups (Figure 2h). The ratio of p-TrkB to total TrkB data revealed significant difference \( F(3,8) = 27.328, P < 0.001 \) among the four groups. The ratio of p-TrkB to total TrkB was significantly lower (\( P < 0.01 \)) in the CUMS rats than in the controls (\( P < 0.001 \); Figure 2i). No significant difference was detected in the ratio of p-TrkB to total TrkB of the CUMS rats after ketamine or a combination of ketamine and ANA-12 administration (Figure 2i).

The effects of knockdown of p11 in the sustained antidepressant-like activity of ketamine

Three different sequences of LV-p11-eGFP were built to silence p11, which were screened by primary neuronal culture (Figures 3a and b). Both LV-A and LV-B, but not LV-C, decreased the expression of p11 in the cultured hippocampal cells (Figure 3c).

One-way ANOVA of p11 data revealed significant differences among the four groups \( F(3,8) = 39.677, P < 0.001 \). The LV-A reduced approximately 32.8% expression of p11, and the LV-B was...
approximately 86.5% (Figure 3c). Therefore, LV-B was selected to knock down the hippocampal p11 in the rats.

To knock down the hippocampal expression of p11 in vivo, the LV-B was bilaterally injected into the DG zone (Figure 4a). The hippocampal injection of LV-B was able to infect the surrounding neuronal cells during the 13-day interval (Figure 4b). The low magnification displayed that the DG region was effectively infected as exemplified by the eGFP+ cells across the entire region, particularly the mossy cell axons. At medium magnification, the heavily infected DG and CA1 regions were evident, and at high magnification, there were neurons and the axons of cells from the DG (the mossy fibers), which transmit information to other cells in the dentate and to area CA3. One-way ANOVA of p11 data revealed significant differences among the four groups (F(3,8) = 10.710, P < 0.01). Compared with the LV-eGFP group, the expression of hippocampal p11 protein was significantly (P < 0.05) decreased in the saline-treated and ketamine-treated groups of LV-B-injected rats on day 13 after LV-p11-eGFP injection (Figure 4c). No significant difference was found in the p11 levels among the saline-treated group and the ketamine-treated group (Figure 4c).

To test the alterations of sustained antidepressant-like effects of ketamine after knockdown, the hippocampal expression of p11 in vivo, open-field test and FST were performed at 72 h and SPT during a 3-day period after the administration of saline or ketamine (Figure 4a). There was no significant difference (F(3,28) = 0.239, P = 0.86) among groups in the total distance of the open-field test (Figure 4d). One-way ANOVA of FST data revealed significant differences among the four groups (F(3,28) = 6.682, P < 0.01). The immobility time of saline-treated and ketamine-treated rats within the LV-B group was significantly (P < 0.05) higher than that of the control and LV-eGFP groups (Figure 4e). One-way ANOVA of SPT data revealed significant differences among the four groups (F(3,28) = 9.271, P < 0.001). The sucrose preference of the saline-treated and ketamine-treated rats within the LV-B group was significantly (P < 0.05) lower than that of the control and LV-eGFP groups (Figure 4f). In the SPT, the total volume consumed among the four groups was not significantly different (F(3,28) = 0.424, P = 0.73; Figure 4g).

**DISCUSSION**

The major findings of the present study are as follows. First, ketamine produced a rapid and sustained antidepressant-like effect in CUMS rats, and the TrkB antagonist ANA-12 significantly blocked the antidepressant effect of ketamine. Second, hippocampal BDNF levels of CUMS rats were significantly lower than those of the control rats, and a single administration of ketamine to CUMS rats could increase hippocampal BDNF to control levels. Third, hippocampal p11 levels of CUMS rats were significantly lower than those of control rats. Ketamine did not alter the expression of p11 in the hippocampus of CUMS rats when measured 0.5 h after administration. However, the expression of p11 in the hippocampus of CUMS rats was recovered to control levels 72 h after ketamine administration. This effect was blocked by co-treatment with ANA-12. Fourth, the expressions of proBDNF and TrkB signaling in the hippocampus of CUMS rats treated with saline, ketamine or a combination of ketamine and ANA-12 had no significant differences compared with the control rats. Fifth, the reduced ratio of p-TrkB to total TrkB in the CUMS rats was improved 0.5 h after ketamine administration, and this effect was blocked by co-treatment with ANA-12. Sixth, the knockdown of p11 in the hippocampus induced depression-like behavior in rats, which was not improved by the administration of ketamine. Altogether, these findings suggest that BDNF–TrkB signaling and p11 in the hippocampus have key roles in the sustained antidepressant effect of ketamine.

Consistent with previous reports, this study found a rapid and sustained antidepressant effect of ketamine in the CUMS model of depression.7–9 Currently, the precise mechanisms underlying the effect of ketamine are still unclear. By blocking the N-methyl-D-aspartate receptors, ketamine-induced glutamate can activate AMPA receptors resulting in the activation of intracellular cascades, including mammalian target of rapamycin, cAMP response element-binding protein and postsynaptic density protein (PSD-95).7,8,15 Multiple studies have suggested a key role of BDNF–TrkB signaling in the pathophysiology of depression and in the therapeutic mechanism of antidepressants.5,34–36 The hippocampal expression of BDNF is decreased in rodent models of depression, and chronic treatment with antidepressants increases BDNF expression in the hippocampus.5,34–36 BDNF is synthesized by the proteolytic cleavage of proBDNF that catalyzed by the plasmin.19 However, it is reported that BDNF and proBDNF show opposite effects on physiological function. ProBDNF preferentially binds to p75 neurotrophin receptors, triggering anti-plasticity and pro-apoptotic actions, while BDNF has high affinity to TrkB receptors, which promotes neuronal cell survival, modulates synaptic plasticity and facilitates hippocampal neurogenesis, all of which are related to the cellular actions of antidepressants.9,33,40 In this study, we found that the hippocampal levels of proBDNF and TrkB had no significant difference among groups, while the levels of BDNF and p-TrkB/TrkB ratio in the hippocampus of CUMS rats were increased at 0.5 h after ketamine administration, indicating that the rapid antidepressant effect of ketamine may be mediated by the stimulation of BDNF–TrkB signaling in the hippocampus. Meanwhile, we also found that hippocampal BDNF levels of CUMS rats were increased at 72 h after ketamine administration. These results suggest that the BDNF–TrkB signaling in the hippocampus has a role in the rapid and sustained antidepressant-like activity of ketamine.

It is reported that BDNF could increase the expression of p11 in primary hippocampal culture, and the increase of p11 protein by 5-HT was attenuated in primary hippocampal culture from BDNF knockout mice.30 Furthermore, the expression of mRNA and protein of p11 in the brain of BDNF knockout mice was significantly lower than that of the wild-type mice.30 Moreover, the p11 knockout mice showed depression-like behavior in the tail suspension test and FST, and BDNF did not show an antidepressant effect in these mice.30 These findings suggest a key role of p11 in the antidepressant effect of BDNF. In this study, we found that the expression of p11 in the hippocampus of CUMS rats was increased at 72 h after a single administration of ketamine; which could be blocked by ANA-12. In contrast, we found that knockdown of p11 in the rat hippocampus produced depression-like behavior and that ketamine did not show antidepressant effects in the rats with knockdown of hippocampal p11. Thus, it is likely that CUMS causes the reduction of BDNF in the hippocampus, followed decreased p11 expression, resulting in depression-like behavior in rats. Furthermore, BDNF–TrkB signaling and p11 in the hippocampus have key roles in the sustained antidepressant effect of ketamine.

Unfortunately, we found no significant alteration of hippocampal p11 at 0.5 h after ketamine administration, suggesting that p11 may not have a role in the rapid antidepressant-like activity of ketamine. Warner-Schmidt et al.30 found that p11 protein was shown to increase at 3 h after BDNF stimulation in primary neural cultures. Therefore, it is unlikely that 0.5 h was sufficient time for the p11 protein to increase after ketamine administration. Meanwhile, Gigliucci et al.31 reported that the reduction of the immobility time of FST by ketamine was blocked by 5-HT depletion when ketamine was administered 24 h, but not 1 h, before FST. These results suggest the role of 5-HT in the sustained antidepressant effect of ketamine. 5-HT and its receptors were also involved in the expression of BDNF by antidepressants.42,43 Interestingly, p11 also interacts with 5-HT receptors, including 5-
HT_{1B}, 5-HT_{1D} and 5-HT_{4} receptors.\textsuperscript{22} Therefore, the relationship between 5-HT receptors and BDNF–TrkB signaling may be involved in the role of p11 in the sustained antidepressant-like activity of ketamine. However, more detailed studies are needed to confirm this hypothesis.

How p11 mediates the therapeutic activity of antidepressants is still unknown. It has been reported that p11 facilitates surface expression of the 5-HT_{1A} and 5-HT_{4} receptors, modulates several cell process and interacts with a number of ion channels and G-protein-coupled receptors.\textsuperscript{20,23,44} Winterer et al.\textsuperscript{45} demonstrated that 5-HT via 5-HT_{1B} receptors reduces the feedback inhibition of interneurons, resulting in an increase in the excitation of CA1 pyramidal cells within the rat hippocampus. However, previous studies have also shown that 5-HT_{4} receptors in the hippocampus are more relevant to the antidepressant-like activity of p11 than 5-HT_{1B} receptors.\textsuperscript{50} This outcome is due to a higher level of 5-HT_{4} receptors in the hippocampus and the inhibited synaptic glutamate currents by activation of the presynaptic 5-HT_{1B} receptor.\textsuperscript{47,49} Therefore, it should be noted that 5-HT_{4} receptors are also identified as the fast-acting antidepressant target.\textsuperscript{49}

The subventricular zone and subgranular zone of the DG are two primary areas of adult neurogenesis.\textsuperscript{52,53} Ketamine produces antidepressant-like activity by increasing neurogenesis within the hippocampus, which is highly sensitive to chronic stress.\textsuperscript{51} A previous research study illustrated that the neurogenic effects of fluoxetine were attenuated in p11 knockout mice, suggesting that p11 might mediate the neurogenesis effects of antidepressants.\textsuperscript{52} Therefore, p11 might also mediate the antidepressant-like activity of ketamine with respect to neurogenesis. However, recent studies have reported that the open-field test and FST were neurogenesis-independent behavioral tests.\textsuperscript{53} Further studies to investigate the neurogenesis-dependent behaviors in the p11-mediated antidepressant-like activity of ketamine are interesting.

Finally, this study has a limitation that need to be mentioned. It is also known that prefrontal cortex and nucleus accumbens are involved in the depression-like phenotype.\textsuperscript{15,54–56} Further studies will be needed to study the role of p11 in these two brain regions for the antidepressant action of ketamine.

In conclusion, the present study suggests that BDNF–TrkB signaling and p11 in the hippocampus have key roles in the sustained antidepressant-like activity of ketamine. Therefore, it is likely that p11 might be a new target for the development of ketamine-like antidepressants.

**CONFLICT OF INTEREST**

KH is an inventor on a filed patent application (pending) on ‘The use of R-ketamine in the treatment of psychiatric diseases’ by Chiba University. KH has served as a scientific consultant to Astellas and Taisho, and he also received the research support from Abbvie, Daiippon Sumitomo, Otsuka and Taisho. The remaining authors declare no conflict of interest.

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