Gene deficiency and pharmacological inhibition of caspase-1 confers resilience to chronic social defeat stress via regulating the stability of surface AMPARs

Both inflammatory processes and glutamatergic systems have been implicated in the pathophysiology of mood-related disorders. However, the role of caspase-1, a classic inflammatory caspase, in behavioral responses to chronic stress remains largely unknown. To address this issue, we examined the effects and underlying mechanisms of caspase-1 on preclinical murine models of depression. We found that loss of caspase-1 expression in Caspase-1−/− knockout mice alleviated chronic stress-induced depression-like behaviors, whereas overexpression of caspase-1 in the hippocampus of wild-type (WT) mice was sufficient to induce depression- and anxiety-like behaviors. Furthermore, chronic stress reduced glutamatergic neurotransmission and decreased surface expression of glutamate receptors in hippocampal pyramidal neurons of WT mice, but not Caspase-1−/− mice. Importantly, pharmacological inhibition of caspase-1-interleukin-1β (IL-1β) signaling pathway prevented the depression-like behaviors and the decrease in surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) in stressed WT mice. Finally, the effects of chronic stress on both depression- and anxiety-like behaviors can be mimicked by exogenous intracerebroventricular (i.c.v.) administration of IL-1β in both WT and Caspase-1−/− mice. Taken together, our findings demonstrate that an increase in the caspase-1/IL-1β axis facilitates AMPAR internalization in the hippocampus, which dysregulates glutamatergic synaptic transmission, eventually resulting in depression-like behaviors. These results may represent an endophenotype for chronic stress-induced depression.

Molecular Psychiatry (2018) 23, 556–568; doi:10.1038/mp.2017.76; published online 18 April 2017
cortex. Meanwhile, dysfunction of glutamatergic neurotransmission in rodents is associated with anhedonia, impaired social interactions (SIs), weight loss, cognitive impairment, behavioral despair and dysregulated feeding behavior. For example, chronic unpredictable mild stress (CUMS) selectively attenuates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) -mediated synaptic transmission in the hippocampus of rats. Chronic administration of AMPA produces antidepressant effects in both the forced swim and sucrose preference test by increasing hippocampal brain-derived neurotrophic factor (BDNF). In addition, GluA1 knockout (Gria1−/−) mice exhibit a depression-like phenotype and increased levels of glutamate in the hippocampus, but not in forebrain excitatory neurons. Collectively, these observations indicate that glutamatergic system is a primary mediator of depression pathology and, potentially, also a final common pathway for the therapeutic action of antidepressant agents.

It has been found that inhibition of caspase-1 significantly enhances AMPAR-mediated long-term potentiation (LTP) without affecting the N-methyl-D-aspartate receptor (NMDAR) -mediated component. Conversely, elevated IL-1β levels decrease the surface expression of AMPARs and inhibits LTP in the hippocampus, and may underlie the pathophysiology of various psychiatric disorders, such as depression, anxiety and addiction. Interestingly, ketamine, a new type of antidepressant that is dependent on the activation of AMPARs, also reduces the levels of proinflammatory cytokines in adult rats following maternal deprivation. Furthermore, recent studies have shown that neuroinflammation regulates CUMS-induced impairment of cognition and LTP by attenuating GluA1 phosphorylation. However, it remains unclear whether there is a causal relationship between caspase-1-mediated regulation of AMPAR-dependent neurotransmission and depression-like behavior.

In this study, we hypothesized that chronic stress may increase the level of caspase-1 in the hippocampus, which would contribute to the internalization of AMPAR, eventually leading to the impairment of synaptic transmission and depression-like behavior (Figure 1a). Thus, we performed a variety of behavioral, immunofluorescence, molecular and electrophysiological experiments to investigate whether the caspase-1 contributes to the induction of depression-like behaviors by regulating the surface stability of AMPARs in animal models.

### MATERIALS AND METHODS

#### Animals

Adult male C57BL/6J mice (7–9 week old, 22–24 g) were purchased from Hunan SJA Laboratory Animal (Changsha, Hunan, China). Both caspase-1 knockout (Caspase-1−/−) and their wild-type (WT) mice on a C57BL/6J genetic background were obtained from Prof. Gang Hu (Nanjing Medical Science and Technology). Animals were bred and maintained in the Animal Laboratory Animals and approved by the Animal Welfare Committee of Huazhong University of Science and Technology.

Mouse behavioral tests

All mouse behavioral tests were recorded using a videotracking system (AniLab software; AniLab Software & Instruments) unless otherwise indicated. All animals were transported to a dimly illuminated behavioral room and were left undisturbed for at least 1 h before testing. Detailed materials and methods of the novel object recognition, sucrose preference test, tail suspension test (TST), forced swim test (FST), measurement of pain threshold, opiate withdrawal test (OWT) and ethanol plus morphine (EPM) were provided in the Supplementary Information. Depression-like behaviors were assessed using SI, sucrose preference test, TST and FST, and OWT and EPM for anxiety-like behaviors. We used multiple behavior testing on the same animals. All animals from different groups were given the same tests in the same order.

Electrophysiological recordings in hippocampal slices

Whole-cell patch-clamp recordings. C57BL/6J (10–12 weeks) mice were anesthetized with isoflurane, and then perfused with 30 ml ice-old oxygenated (95% O2 and 5% CO2) dissection buffer that contained (in mM): 210 sodium chloride, 3.1 sodium pyruvate, 11.6 sodium L-ascorbate, 1.0 NaH2PO4, 26.2 NaHCO3, 5.0 MgCl2 and 20.0 glucose, pH 7.4 (300 mM). Brains were removed rapidly into oxygenated chilled dissection buffer. Coronal hippocampal slices (300 μm) were prepared using a vibratome (VT 1000 S, Leica, Wetzlar, Germany), and the slices were incubated for 30 min.
at least 1.5 h in an interface chamber containing artificial cerebrospinal fluid that consisted of (in mM): 119.0 NaCl, 3.5 KCl, 1.3 MgSO₄, 2.5 CaCl₂, 1.0 NaH₂PO₄, 26.2 NaHCO₃ and 11.0 glucose, pH 7.4 (300 mOsm). Whole-cell voltage-clamp recordings of CA1 pyramidal cells were made in a submersion chamber with patch electrodes (3-6 MΩ resistance) filled with a solution containing (in mM): 122.5 Cs-gluconate, 17.5 CsCl, 0.2 EGTA, 10.0 HEPES, 1.0 MgCl₂, 4.0 Mg-ATP, 0.3 Na-GTP, and 5.0 QX314, pH 7.2 (280-300 mOsm). AMPAR-mediated miniature excitatory postsynaptic current (mEPSC) was isolated by including bicuculline (20 μM) and tetrodotoxin (1 μM) in the bath solution. All recordings were performed at a holding potential of -70 mV with a Multiclamp 700B amplifier (Molecular Devices, Sunnyvale, CA, USA) under an upright Olympus microscope (BX51WIF, Olympus, Tokyo, Japan) at room temperature. Data was filtered at 2 kHz and sampled at 10 kHz using Digidata 1322A digitizer (Molecular Devices), and then was acquired with pClamp 10 software. Data was analyzed by Mini Analysis Program (Synaptosoft, Decatur, GA, USA) with an amplitude threshold of 5 pA for mEPSC analysis.

Field potential recording. Brain slices were obtained according to our previous studies with some modifications. Briefly, the brain was removed immediately after the anaesthetized animal was decapitated and coronal hippocampal slices (350 μm) were cut using Leica VT 1000 S vibratome in

Chronic Social Defeat Stress

h

Time in interaction zone (%)  
No target  Target  
Stress  

Sucrose preference (%)  
Stress  

Discrimination index  
Fami (pretest) Novel (test)  

Chronic Restriction Stress

k

Sucrose preference (%)  
Stress  

Immobility time (s)  
FST  

Immobility time (s)  
TST
ice-cold artificial cerebrospinal fluid. After 1.5 h of recovery at room temperature, an individual slice was transferred to a submerged recording chamber and continuously superfused with oxygenated artificial cerebrospinal fluid at 30 ± 1 °C at a rate of 2–4 ml min⁻¹. Field excitatory postsynaptic potentials (fEPSPs) were evoked by a constant stimulation in the Schaffer collaterals with a bipolar stimulating electrode and recorded in the stratum radiatum layer of CA1 region with a glass micropipette (3–5 MΩ resistance) filled with 3 M NaCl. Test frequency to evoke fEPSPs was 0.03 Hz. The amplitude of the fEPSPs was usually set at 30–35% of maximal responses. The input–output relationship for synaptic transmission was recorded by stimulating Schaffer collateral-CA1 afferents with increasing levels of intensity. When paired-pulse facilitation was determined, paired stimuli (25, 50, 75, 100 and 200 ms intervals) were delivered and the ratio of the slope of the second fEPSP (fEPSP2) over the first fEPSP was determined. After recording of stable baseline for at least 20 min, LTP was induced by three trains of high-frequency stimulation (HFS: 100 pulses at 100 Hz separated by 30 s), LTD was induced by single-pulse low-frequency stimulation (LFS: 900 pulses at 1 Hz for 900 s) and the stimulation intensity was adjusted to give fEPSP slopes of ~50% of maximum. The fEPSP was monitored for 60 min and the fEPSP slopes were normalized to the average of the slopes of the fEPSPs acquired during the baseline. All data were calculated as the average of the last 15 min out of 60 min recordings.

Western blotting and other experiments. Western blotting was performed according to a protocol that is routinely used in our laboratory. The surface expression of NMDARs and AMPARs was assayed by BS 3 crosslinking (5 or 10 μM) according to a protocol that is routinely used in our laboratory. The surface transcardially, and serial brain sections were made. Fluorescence microscopy for 10 days. This dose of IL-1ra blocks depression-like behaviors ± mean ± s.e.m., repeated-measures ANOVA, Bonferroni comparison tests. Statistical analyses were performed using unpaired Student’s t-tests, one or two-way analysis of variance, or repeated-measures analysis of variance, where appropriate. Significant effects in analysis of variances were followed by Bonferroni’s post hoc multiple comparison tests. P < 0.05 was considered statistically significant.

RESULTS

Genetic ablation of caspase-1 in mice prevents chronic stress-induced depression-like behaviors

To identify the relevance of caspase-1 and different stressors, which are well recognized to mimic the precipitating factors of MDD, we first employed CSDS, CUMS animal model of depression. Following exposure to CSDS, C57BL/6J mice were separated into susceptible and resilient subpopulations (Figure 1b and Supplementary Figures 1 and 2a). Susceptible mice displayed a significant decrease in sucrose preference, body weight and memory impairment (Figure 1c and Supplementary Figures 2b–d) when compared with non-defeated control mice. As shown previously, there was no change in serum corticosterone levels induced by CSDS (Supplementary Figure 2e), whereas both susceptible and resilient mice displayed a corticosterone response after a 6 min swim stress test following CSDS (Supplementary Figure 2f). Meanwhile, CUMS-treated mice also showed depression-like behavior, such as decreased sucrose preference and increased immobility time in TST (Supplementary Figures 2g and h).

Next, the levels of caspase-1 were examined under different stressors. We found that caspase-1 mRNA was significantly increased in the periphery blood mononuclear cell and hippocampus of susceptible mice induced by CSDS compared with control mice (Figure 1d), but remained unchanged in the striatum and amygdala (Supplementary Figure 2i). Moreover, we observed a significant negative correlation between the level of caspase-1 mRNA and SI ratio (Figure 1e). Furthermore, in contrast to control mice, susceptible mice displayed a significant increase in the level of the activated form of caspase-1 protein in the hippocampus (Figure 1f). However, caspase-1 protein levels were not increased in the thalamus or amygdala of susceptible mice (Supplementary Figure 2j), confirming the regional specificity of chronic stress-induced changes in caspase-1. Meanwhile, CUMS also significantly upregulated the level of cleaved form of caspase-1 protein in the hippocampus (Figure 1g).
To determine the effect of caspase-1 on the depressive-like behavior induced by different stressors, the C57BL/6J mice with a genetic ablation of caspase-1 (Caspase-1\(-/-\)) was used. Calcium/calmodulin-dependent protein kinase type II (CaMKII) signaling and the gross morphology of the hippocampus were unaffected by loss of caspase-1 (Supplementary Figures 3 and 4). Under non-stressed conditions, Caspase-1\(-/-\) mice, but not WT control mice, showed anxiolytic behavior in the OF and EPM tests (Supplementary Figure 5). When compared with WT mice, caspase-1\(-/-\) mice did not display differences in total fluid intake, sucrose consumption, vocalizing and jumping (Supplementary Figures 6a-c), but did exhibit increased locomotion (Supplementary Figure 6d).

We then compared Caspase-1\(-/-\) with WT mice in the CSDS model. Under non-defeated conditions, baseline SI and sucrose consumption of Caspase-1\(-/-\) mice were similar with those of WT littermates. Different from WT-CSDS mice, Caspase-1\(-/-\) mice exposed to CSDS showed increased body weight gain, SI and sucrose consumption (Figures 1h and i and Supplementary Figures 6a-d). Furthermore, impaired recognition memory was only observed with WT-CSDS mice (Figure 1j), which did not display a difference in the exploration time for the novel preference value of the novel object (Supplementary Figure 7e).

Next, Caspase-1\(-/-\) mice and their WT littermates were subjected to CRS. Compared with non-stressed control mice, WT-CRS mice displayed depression-like behaviors, including decreased sucrose consumption and increased immobility time in FST and TST (Figures 1k-m and Supplementary Figure 7f). Strikingly, the depression-like behaviors induced by CRS in WT mice were completely prevented in the Caspase-1\(-/-\) mice (Figures 1k-m and Supplementary Figure 7f). Moreover, serum corticosterone levels were higher in both CRS-treated groups when compared with controls (Supplementary Figure 7g), which was consistent with a previous study.42 Taken together, these findings confirm that Caspase-1\(-/-\) mice are resilient to chronic stress-induced depression-like behaviors.

Caspase-1 overexpression in the hippocampus increases depression- and anxiety-like behaviors

Next, we used a viral expression approach to examine whether the overexpression of caspase-1 in hippocampus is responsible for the behavioral effects of CSDS (Figure 2a). We stereotaxically injected an AAV serotype 1 vector encoding caspase-1 (AAV-caspase-1) into the hippocampus. The accuracy of the injection site was confirmed by immunofluorescence staining of GFP, which is co-expressed with caspase-1 by the AAV (Figure 2b and Supplementary Figure 8a). AAV-caspase-1 infusion resulted in significantly increased levels of caspase-1 and IL-1β protein (Figure 2c). We found that AAV-caspase-1 mice showed a significant decrease in SI and sucrose preference following subthreshold social defeat stress (Figures 2d and e and Supplementary Figures 8b-d) compared with control virus-injected mice (AAV-GFP). Further, AAV-caspase-1 mice displayed increased immobility time in the TST and FST compared with AAV-GFP mice (Figure 2f). The velocity or total distance traveled was not affected in AAV-caspase-1 mice (Supplementary Figure 8e), indicating that immobility was not likely due to motor defects. There is strong comorbidity between anxiety disorders and depression, and AAV-caspase-1 mice also displayed an anxiogenic phenotype. Compared with AAV-GFP mice, AAV-caspase-1 mice spent less time, distance traveled, and fewer visits in the central area of the OF (Figure 2g and Supplementary Figures 8e and g), and less time in the open arms and conversely more time in the closed arms in the EPM (Figure 2h and Supplementary Figures 8f and h). Together, these results suggest that caspase-1 overexpression in the hippocampus induces depression- and anxiety-like behaviors.

Genetic ablation of caspase-1 blocks CSDS-induced synaptic plasticity impairment in the hippocampus

Accumulating evidence suggests that chronic stress causes changes in the glutamatergic system, and dysregulation of glutamate signaling is increasingly considered to be a core feature of mood disorder.1,12,13,43 To investigate the role of caspase-1 in glutamate neurotransmission, we first examined the input/output curves in the CA1 region of hippocampal slices. The input/output curves were markedly reduced in the WT-CSDS group but remained unaffected in the Caspase-1\(-/-\)-CSDS group (Figure 3a). No significant differences were observed in paired-pulse facilitation (Supplementary Figures 9a and b), suggesting a lack of gross change in presynaptic function in Caspase-1\(-/-\) mice. Compared with WT mice, Caspase-1\(-/-\) mice showed a normal induction and maintenance of LTP in Schaffer collateral-CA1 after CSDS (Figure 3b), but there was no change in NMDAR-dependent LTD (Supplementary Figures 9c and d). To determine if the suppression of CSDS on glutamatergic neurotransmission results from the reduced expression of glutamate receptors, we performed western blotting and surface receptor crosslinking with BS3 in primary cortical cultures. Following exposure to CSDS, Caspase-1\(-/-\) mice showed increased surface expression of GluA1 and GluA2 in the hippocampus compared with WT mice (Figure 3c). In addition, the total levels of AMPARs and NMDARs, and the surface expression of NMDARs, were unaltered in all groups (Figure 3d and Supplementary Figure 10). Furthermore, Caspase-1\(-/-\) mice completely blocked the reduction of PSD95 caused by CSDS in WT mice (Figure 3d), indicating CSDS-induced synaptic dysfunction is unique to excitatory glutamatergic neurons, but not GABAergic interneuron. Next, we measured mEPSCs in CA1 pyramidal neurons, which are mediated by AMPARs and reflected the individual synaptic responses from the quantal release of single glutamate vesicles. WT mice exposed to CSDS showed a greatly decreased mEPSC amplitude, which remained unchanged in the Caspase-1\(-/-\) mice upon exposure to CSDS. Furthermore, there were no effects of CSDS on mEPSC frequency in both mice (Figure 3e). In addition, CSDS significantly reduced the density of PSD95 immunofluorescence in WT but not in Caspase-1\(-/-\) mice (Figure 3f and Supplementary Figure 11), consistent with the observation that hippocampal neurons were not lost in these mice after chronic stress.44 These results suggest that the deletion of caspase-1 increases the resilience to chronic stress by maintaining normal postsynaptic glutamate neurotransmission.

Interestingly, only susceptible mice showed a significant increase in serum IL-1β compared with control mice (Supplementary Figure 12a). It is well established that IL-1β is a downstream target of caspase-1, and that IL-1β maturation depends on caspase-1 activation.34 Thus, we examined the effect of caspase-1 loss on IL-1β levels. As shown by ELISA, CSDS increased the level of serum IL-1β in WT mice, but not in Caspase-1\(-/-\) mice (Figure 3g). Furthermore, ablation of caspase-1 prevented the CSDS-induced elevation of IL-1β mRNA and protein levels in the hippocampus (Figures 3h and i).

Inflammasome cleaves pro-caspase-1 into mature caspase-1, which subsequently mediates the maturation of IL-1β. Therefore, we tested whether inflammasomes modulate CSDS-induced depression. CSDS exposure increased the mRNA level of nucleotide-binding oligomerization domain-like receptor pyrin domain-containing protein 3 (NLRP3) in WT and Caspase-1\(-/-\) mice, but not of NLRP1 and absent in melanoma 2 mRNA (Supplementary Figures 12b-d). Interestingly, CSDS failed to increase the expression of apoptosis-associated speck-like protein containing a CARD (ASC) mRNA in Caspase-1\(-/-\) mice compared with WT mice (Supplementary Figure 12e). These results indicate that CSDS activates the NLRP3 inflammasome, leading to the increased release of caspase-1-dependent IL-1β. IL-1β can suppress BDNF-dependent synaptic plasticity via the p38 mitogen-activated pathway.
Further, our previous study showed that CSDS significantly reduced the expression of BDNF in the hippocampus of susceptible mice. Thus, we evaluated whether CSDS could change the levels of phosphorylated p38 MAPK and BDNF in Caspase-1−/− mice. As predicted, phosphorylation of p38 MAPK was significantly elevated and BDNF was decreased in the WT-CSDS group; however, their levels were unaltered in the Caspase-1−/−-CSDS group (Figure 3i).

AAV, adeno-associated virus; ANOVA, analysis of variance; CMV, cytomegalovirus; EPM, elevated plus maze; FST, forced swim test; GFP, green fluorescent protein; OF, open-field test; TST, tail suspension test.
together, these results suggest that caspase-1-mediated neuroinflammation affects glutamatergic neurotransmission, leading to CSDS-induced depression-like behaviors.

Pharmacological inhibition of the caspase-1 signaling pathway prevents CSDS-induced depression-like behaviors and synaptic impairment

Next, we examined the effect of the caspase-1-specific inhibitor AC-YVAD-CMK on depression-like behaviors. A single intracerebroventricular (i.c.v.) microinfusion of AC-YVAD-CMK significantly decreased immobility time of mice in a dose-dependent manner in FST as well as TST without affecting locomotion (Supplementary Figures 13a and b). Thus, acute caspase-1 inhibitor treatment produces antidepressant-like effects in mice. Further, we found that WT-CSDS mice repeatedly pretreated with AC-YVAD-CMK exhibited normal SI and sucrose preference compared to control mice (Figure 4a and Supplementary Figures 13c–e), confirming the effect of AV-YVAD-CMK on CSDS-induced depressive behaviors. Moreover, AC-YVAD-CMK treatment also prevented the increase in caspase-1 and IL-1β expression (Figure 4b), as well as the

Figure 3. Genetic ablation of caspase-1 blocks CSDS-induced synaptic plasticity impairment in the hippocampus. (a) Input–output curves illustrating the relationship between the magnitudes of stimulation and evoked response for fEPSPs recorded in hippocampal slices from WT, WT-CSDS, Caspase-1−/− and Caspase-1+/− CSDS groups. Insets are typical superimposed fEPSPs recorded by increasing stimulation intensity (n = 10 slices from four to seven mice per group, mean ± s.e.m., repeated-measures ANOVA, Bonferroni’s test, *P < 0.05). (b, left) Time-course of LTP induced by HFS in hippocampal slices from different groups. Insets are superimposed fEPSPs recorded for each condition before (1) and 60 min after the application of HFS (2). (right) The histogram showing LTP magnitude averaged from the last 15 min of recordings from different groups (n = 8–11 slices from four to seven mice per group, mean ± s.e.m., two-way ANOVA, Bonferroni’s test, *P < 0.05, **P < 0.01, ***P < 0.001). (c) Representative immunoblots and quantification of surface expression of GluA1 and GluA2 in the hippocampus from different groups (n = 7 mice/group, mean ± s.e.m., two-way ANOVA, Bonferroni’s test, *P < 0.05, **P < 0.01). (d) Representative immunoblots and quantification of total expression of hippocampal GluA1, GluA2 and PSD95 proteins from different groups (n = 6–7 mice/group, mean ± s.e.m., two-way ANOVA, Bonferroni’s test, *P < 0.05, **P < 0.01). (e, left) Representative whole-cell voltage-clamp traces of AMPAR-mediated mEPSC in the hippocampal pyramidal neurons. Scale is depicted on the middle right. (right) Mean ± s.e.m. amplitude and frequency of AMPAR-mediated mEPSC from different groups (n = 10–12 cells from five to six mice per group, mean ± s.e.m., two-way ANOVA, Bonferroni’s test, *P < 0.01). (f) Immunofluorescence of PSD95 in CA1 pyramidal neurons. Scale bars, 100 μm. (g) The levels of IL-1β in the serum were determined by ELISA in the different groups (n = 10–12 mice/group, mean ± s.e.m., two-way ANOVA, Bonferroni’s test, ***P < 0.001). (h) Analysis of IL-1β mRNA expression in the hippocampus by qRT-PCR. (n = 5 mice/group, mean ± s.e.m., two-way ANOVA, Bonferroni’s test, ***P < 0.001). (i) Representative immunoblots and quantification of hippocampal IL-1β, p-p38 MAPK and BDNF proteins (n = 6–7 mice/group, mean ± s.e.m., two-way ANOVA, Bonferroni’s test, *P < 0.05, **P < 0.01). AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANOVA, analysis of variance; BDNF, brain-derived neurotrophic factor; CSDS, chronic social defeat stress; fEPSP, field excitatory postsynaptic potential; HFS, high-frequency stimulation; I, intracellular; IL, interleukin; LTP, long-term potentiation; mEPSC, miniature excitatory postsynaptic current; S, surface; qRT-PCR, quantitative PCR with reverse transcription; WT, wild-type.
reduction of surface levels of GluA1 and GluA2, in response to CSDS (Figure 4c). There was no significant difference in the total levels of GluA1 and GluA2 (Supplementary Figure 13f). Furthermore, we observed a decrease in the amplitude of mEPSC in CSDS-treated mice, but not in CSDS-AC-YVAD-CMK-treated mice, and the frequency of mEPSC remained unchanged (Figure 4d and Supplementary Figure 13g), confirming that pharmacological inhibition of caspase-1 prevents CSDS-induced depression-like behaviors and the impairment of synaptic plasticity.

To further confirm a direct role of caspase-1-mediated IL-1β signaling pathway in CSDS-induced depression-like behaviors, we next investigated whether the blockade of IL-1β could prevent depression in WT-CSDS mice. Although a single i.c.v. infusion of recombinant mouse IL-1ra had no effect on sucrose preference, locomotion and anxiety behaviors (Supplementary Figures 14a–c), repeated i.c.v. infusions of IL-1ra prevented CSDS-induced social avoidance and sucrose preference reduction in a dose-dependent manner (Figure 4e and Supplementary Figures 14d–f). Consistent with these behavioral results, IL-1ra also blocked the decrease in surface expression of GluA1 and GluA2 caused by CSDS, whereas the total proteins levels remained unchanged (Figures 4f and g). Furthermore, IL-1ra not only reduced the expression of reduction of surface levels of GluA1 and GluA2, in response to CSDS (Figure 4c). There was no significant difference in the total levels of GluA1 and GluA2 (Supplementary Figure 13f). Furthermore, we observed a decrease in the amplitude of mEPSC in CSDS-treated mice, but not in CSDS-AC-YVAD-CMK-treated mice, and the frequency of mEPSC remained unchanged (Figure 4d and Supplementary Figure 13g), confirming that pharmacological inhibition of caspase-1 prevents CSDS-induced depression-like behaviors and the impairment of synaptic plasticity.

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phosphorylated p38 MAPK and increased the levels of BDNF and PSD95 in CSDS-treated mice (Figure 4g), but also prevented the reduction of mEPSC amplitude caused by CSDS, with no effect on mEPSC frequency (Figure 4h and Supplementary Figure 14g). Taken together, these results further suggest that the inhibition of the caspase-1 signaling pathway prevents CSDS-induced depression-like behaviors by stabilizing the surface expression of AMPARs in the hippocampus.

Chronic IL-1β exposure induces depression and anxiety-like behaviors in Caspase-1−/− mice

Previous studies demonstrate that chronic subcutaneous administration of IL-1β can mimic the effects of CUMS-induced depression.28 Thus, we investigated whether chronic central administration of IL-1β could block the antidepressant effect of caspase-1 deletion. Following IL-1β administration for 10 days (Figure 5a), there were no changes in the body weights of either WT or Caspase-1−/− mice (Figure 5b). Interestingly, chronic i.c.v. infusion of IL-1β significantly decreased SI in both WT and Caspase-1−/− mice on days 6 and 11, whereas no difference in SI was observed on day 1 (Figures 5c and d and Supplementary Figure 15a). Consistent with these results, both WT and Caspase-1−/− mice exhibited a significant decrease in sucrose preference on days 10 and 12 (Figure 5e and Supplementary Figure 15b), suggesting that caspase-1-dependent IL-1β production may mediate chronic stress-induced depression-like behaviors.

Furthermore, chronic i.c.v. infusion of IL-1β reduced the number of entries and time spent in the central area in the OF (Figure 5f), shortened the time spent in the open arms and prolonged the time spent in the closed arms in the EPM (Figure 5g). However, there was no effect observed on locomotion, total distance traveled, total arm entries into any arms or open arm entry counts (Supplementary Figures 15c−d), indicating that IL-1β is essential for caspase-1-mediated depression- and anxiety-like behaviors.

DISCUSSION

Caspase-1 has usually been recognized as an inflammatory caspase that is involved in the general response to inflammatory stimuli. In this study, to the best of our knowledge, we have provided direct evidence that, in addition to the classical effects on cytokine maturation and the center of many cell responses to inflammation, caspase-1-mediated surface stability of AMPAR in the hippocampus was essential for the synaptic plasticity impairment and depression-like behavior in response to chronic stress. We showed that loss of caspase-1 caused antidepressant-like effects in mice, and conversely, that overexpression of caspase-1 in the hippocampus of WT mice induced depression- and anxiety-like behaviors. Pharmacological inhibition of the caspase-1-IL-1β signaling pathway protected against CSDS-induced depression. Importantly, we found that inhibition of either caspase-1 or IL-1β could prevent the decrease in surface expression of AMPARs and AMPAR-mediated mEPSC caused by CSDS. Further, caspase-1-activated IL-1β signaling, followed by transcriptional downregulation of BDNF, eventually contributed to impaired synaptic plasticity (Supplementary Figure 16). Our results further provide a rigorous analysis of the convergence of the inflammation and glutamate hypotheses of depression.

We developed an approach to investigate the critical role of caspase-1 in the development of depression. Briefly, we divided the mice exposed to various stressful stimuli, and enabled further establishment of several lines of evidence supporting a critical role of caspase-1 in the active and adaptive development of chronic stress-induced depression. We found that the level of caspase-1 was increased in the periphery after social defeat in susceptible mice. Meanwhile, we demonstrated that Caspase-1−/− mice were resilient to chronic stress without changes in the gross neuroanatomy and morphological structure of the hippocampus. Furthermore, a caspase-1-specific inhibitor displayed an antidepressant effect. Interestingly, glucocorticoid levels are dramatically elevated in depressed patients and animals;38 however, we found that corticosterone was not involved in the caspase-1-mediated depression induced by CSDS. Taken together, these results indicate that caspase-1 has an essential role in the depression, and the level of caspase-1 in the peripheral blood mononuclear cells may be a reliable biomarker for depression.

Caspase-1 regulates food intake and memory through affecting IL-1β processing.29,50 Moreover, Caspase-1−/− mice showed impaired processing of pro-IL-1β and reduced secretion of IL-1β after lipopolysaccharide stimulation.39 Thus, the maturation of IL-1β is one of the main mechanisms whereby caspase-1 regulates behavioral alteration. Consistent with these findings, our results showed that chronic infusion of IL-1β not only abolished the antidepressant-like effects in Caspase-1−/− mice, but also increased anxiety in both WT and Caspase-1−/− mice. Importantly, chronic infusion of specific caspase-1 inhibitor AC-YVAD-CMK prevented CSDS-induced depression-like behaviors and synaptic dysfunction of susceptible mice via suppression of IL-1β expression, as confirmed by administration of IL-1ra, indicating that activated caspase-1 results in increased depression- and anxiety-like behaviors in an IL-1β-dependent manner.

Caspase-5, a component of the NLRP1 inflammasome, mediates the generation of active IL-1β.31,51 It has been shown that chronic glucocorticoids exposure increases hippocampal caspase-5.53 However, our results showed that CSDS robustly increased the level of NLRP3 mRNA, the major contributor to caspase-1 activation and chronic stress-induced depression,11,54,55 without effect on NLRP1 mRNA, suggesting that caspase-5 may not be required to elicit depression-like behaviors. Further, NLRP3 activates caspase-1 in an ASC-dependent manner. ASC levels are significantly elevated in peripheral blood mononuclear cells from depressed patients and in the hippocampus of mice exposure to chronic glucocorticoids.53,56 However, our results showed that ASC mRNA was unaltered in Caspase-1−/− mice after CSDS, indicating that ASC may be not required for CSDS-induced caspase-1 activation and depression. Notably, recent work has demonstrated that deletion of any gene in the NLRP3-caspase-1-IL-1β axis reduces anxiety and depression-like behavior by EPM, OF and dark-light-box test.8,47,55,57 We will further confirm the effects of caspase-1 inhibition by using dark−light-box and learned helplessness paradigm.
Recent studies suggest that the changes in excitatory synapses are a fundamental pathophysiology of depression, and that restoration of synaptic plasticity impairment is critical to the relief of depression.\textsuperscript{12,18,19} Recent studies reveal that genetic ablation of the vesicular transporter 1 (VGLUT1) not only mimic exclusively mood disorder but also induce abnormalities associated with schizophrenia through regulation of presynaptic glutamatergic neurotransmission.\textsuperscript{58–60} Moreover, stress-induced depressive behaviors are associated with altered expression of VGLUT1.\textsuperscript{61,62} Indeed, our results not only support a glutamate hypothesis of

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\textbf{Caspase-1 KO prevents depressive-like behavior}

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**Molecular Psychiatry (2018), 556 – 568**
proinflammatory action of caspase-1/IL-1β signaling pathway. Our study couples the inflammatory caspase-1 signaling pathway with depression-like behavior via modulation of AMPAR trafficking and synaptic plasticity. Taken together, these results suggest that caspase-1 is critical for the development of depression-like behaviors, and highlights caspase-1 as a potential novel therapeutic target for the treatment of mood disorders.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGMENTS
This work was supported by grants from the National Basic Research Program of China (the 973 Program, No. 2013CB531303 to JG; No. 2014CB744601 to FW), The National Natural Scientific Foundation of China (NSFC, No. 81473198, 81673414 to JGC; No. 81471377 to FW), The Innovation Group of Natural Science Fund of Hubei Province (No. 2015CFA020), PCSIRT (No. IRT13016) and the Fundamental Research Funds for the Central Universities, HUST (2015ZTD004) to JGC.

AUTHOR CONTRIBUTIONS
MXL, GH, FW and JGC conceived and designed the project and wrote the manuscript, MXL, HLZ, JGH, JH, LZ, XW, HW, HYZ performed the behavioral experiments, MXL and YL performed the electrophysiology, MXL and HLZ performed the immunohistochemistry. MXL performed the biochemical measurements.

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