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# Downregulation of AdipoR1 in the hippocampus impairs synaptic function and structure and causes depression-like behavior

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Previous studies have indicated that impaired synaptic plasticity is a main pathological alteration in depression. However, the mechanism underlying this pathological change has not been clarified. Adiponectin, an adipokine, crosses the blood–brain barrier to function in specific brain regions. Previous studies have suggested that the downregulation of adiponectin signaling is involved in the occurrence of depression. The adiponectin receptors (AdipoRs) AdipoR1 and AdipoR2, which serve as the main receptors for adiponectin in the central nervous system, mediate the downstream biological effects of this compound, which has been reported to have positive effects on synaptic plasticity. However, it is not clear whether alterations in adiponectin/AdipoR signaling are associated with impaired synaptic plasticity in depression. Therefore, the aim of this study was to investigate whether changes in the adiponectin/AdipoR pathway in the hippocampus during depression are involved in the regulation of synaptic plasticity damage. We detected reduced plasma concentrations of adiponectin and lower expression levels of AdipoR1 but not AdipoR2 in the hippocampi of mice exposed to chronic unpredictable stress. An adeno-associated virus was subsequently used to knockdown hippocampal AdipoR1 to further verify the effects of decreased expression levels of this receptor on depressive-like behaviors and hippocampal synaptic plasticity. We found that the mice in which hippocampal AdipoR1 was knocked down presented with anhedonia and passive stress-coping behaviors as well as a decreased number of dendritic spines and density of excitatory and inhibitory synapses. Our results suggest that the downregulation of AdipoR1 expression might be an important factor that causes impaired synaptic plasticity in depression. These results may provide new insights into the pathogenesis of depression and new therapeutic targets for treating this disease.

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## INTRODUCTION

Depression is a common mental disorder characterized by a prolonged depressed mood and anhedonia [1]. Approximately 350 million people worldwide are estimated to suffer from depression [2]. Importantly, patients with depression often experience suicidal ideation or attempt suicide, and suicide is the second leading cause of death among people aged 15–29 years globally [3, 4]. In recent years, although many treatments for depression have emerged, the side effects of these treatments and the high recurrence rate of depression limit their clinical efficacy [5]. Therefore, the pathogenesis of depression requires further investigation to identify more targets and effective treatments.

The hippocampus is a key brain region involved in depression [6]. Synaptic plasticity in the hippocampus is considered an important mechanism involved in emotion regulation [7]. Duric et al. demonstrated through examination of the postmortem genetic profiles of depressed subjects that the expression of genes related to hippocampus-related synaptic function was significantly downregulated [8]. Willard et al. reported that postsynaptic density protein expression was decreased in the CA1 region of depressed monkeys [9]. This evidence suggests the presence of impaired synaptic transmission and synaptic functional plasticity in the hippocampus in depression. In terms of synaptic structure, the connections between neurons are formed mainly from dendritic spines, which are the predominant sites of information processing in the brain [10]. Loss of dendritic spines and synaptic connection dysfunction are structural deficits thought to be caused by depression [11, 12]. Autopsy studies have revealed that depressed patients have reduced numbers of synapses in the dorsolateral prefrontal cortex (dlPFC) and the hippocampus [13, 14]. Both clinical and basic studies have demonstrated that

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depression is associated with decreased neuronal synapses in the hippocampus and that antidepressants can block or reverse these neuronal deficits [15]. In addition, Moda-Sava et al. reported that depression-related behaviors are associated with targeted, branch-specific elimination of postsynaptic dendritic spines on neurons and that spinogenesis plays a critical role in sustaining specific antidepressant behavioral effects and maintaining long-term behavioral remission [16]. In summary, impairments in the morphological structure and function of synapses in the hippocampus are among the main pathological changes associated with depression. However, the regulatory mechanism underlying the changes in synaptic structure and function in depression is still unclear.

Adiponectin, a circulating hormone released mainly by peripheral adipocytes, is stored in the blood in the form of full-length trimers, hexamers, or spheres [17]. Clinical evidence suggests that adiponectin plasma concentrations are reduced in patients with depression [18–20]. A rodent study also revealed that a reduction in adiponectin levels could increase susceptibility to social aversion, anhedonia and learned helplessness [21]. Intracerebroventricular (i.c.v.) injection of an adiponectin neutralizing antibody precipitated stress-induced depressive-like behavior [21]. Conversely, i.c.v. or intraperitoneal (i.p.) injection administration of exogenous adiponectin produced antidepressant-like behavioral effects in mice [22, 23]. These studies suggest that adiponectin levels are strongly associated with changes in depression-like behavior.

Studies have shown that adiponectin can cross the blood–brain barrier and enter the cerebrospinal fluid (CSF), mainly in the form of spherical trimers [24, 25], and bind to its receptors (AdipoRs, including AdipoR1 and AdipoR2) to affect the central nervous system [26, 27]. Yamauchi et al. reported that AdipoR1 has a significantly greater affinity for globular adiponectin than AdipoR2 does [27]. Thus, the function of spherical adiponectin in the CNS may be mediated by AdipoR1. It has been reported that AdipoR1 is distributed mainly in the cerebral cortex, hippocampus, and amygdala [28]. In our previous study, when an adeno-associated virus (AAV) was used to knockdown hippocampal AdipoR1, mice exhibited depressive-like behaviors [29]. Selective deletion of AdipoR1 in dopaminergic neurons also induced anhedonia in male mice [30]. Therefore, AdipoR1 may be an important receptor for adiponectin in the context of regulating depression-like behavior. It has also been reported that adiponectin can promote hippocampal synaptic plasticity [31]. Moreover, adiponectin signaling through AdipoR1 has beneficial effects on brain metabolism which has been implicated in the regulation of hippocampal synaptic plasticity [32]. Therefore, we hypothesized that changes in the adiponectin/AdipoR1 pathway might be involved in the regulation of changes in synaptic plasticity in depression.

To test our hypothesis, we investigated changes related to synapses and the adiponectin/AdipoR1 pathway in the hippocampus after chronic unpredictable stress (CUS) intervention. We subsequently used an AAV to reduce the levels of hippocampal AdipoR1 in the mice, and assess behavioral and structural/functional changes in hippocampal synapses.

## MATERIALS AND METHODS

### Animals

Five- to seven-week-old male C57BL/6 J mice (weighing 15–20 g) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). All the mice were raised in a room at a temperature of 22 ± 2 °C and a humidity of 56 ± 10% under a 12-h light/12-h dark cycle with free access to food and water. Four or five mice were housed per cage, and bedding was changed every week during the period of adaptive feeding. All procedures of the experiment were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Ethics Committee of Chongqing Medical University. All the mice were allowed to habituate to the housing conditions for 2 weeks before the experiment.

### Experimental design

Mice were randomly assigned to different experimental groups as described below. The timelines of the two different experiments are shown in the experimental diagrams.

*Experiment 1*. To explore the pathology of depression, CUS was used to mimic the major behavioral features of depression [33]. Adult male C57BL/6 J mice were randomly divided into a control group ($n = 19$) and a CUS group ($n = 23$) after adaptive feeding. The control group mice were raised under normal conditions for 4 weeks without any intervention. The CUS group mice were subjected to different types of stressors for four successive weeks. The behavioral tests were performed 24 h after the last stress procedure.

*Experiment 2*. To verify the role of the hippocampal adiponectin/AdipoR1 pathway in the development of depressive-like behaviors and synaptic plasticity, hippocampal AdipoR1 was knocked down via the stereotactic injection of an AAV into the bilateral hippocampi of otherwise healthy mice. After adaptive feeding, adult male C57BL/6 J mice were randomly divided into an AAV-normal control (AAV-Control) group ($n = 13$) and an AAV-AdipoR1 knockdown (AAV-AdipoR1-KD) group ($n = 13$). The mice in the AAV-Control group were injected with AAV-U6-shRNA-CMV-EGFP (siRNA:TTCTCCGAACGTGTCACGTAA, titer $1.32 \times 10^{13}$ vg/mL), and the mice in the AAV-AdipoR1 KD group were injected with AAV-U6-shRNA-AdipoR1-CMV-EGFP (siRNA:GGGACTGCTGTGTGTGTTGTA, titer $8.16 \times 10^{12}$ vg/mL). The AAV was purchased from Hanbio Biotechnology Co., Ltd. (Shanghai, China). The behavioral tests were performed 4 weeks after virus injection.

### Additional methods and materials

See the Supplementary Methods and Materials and Supplementary Tables 1–2 for descriptions of the other methods, materials and statistical analyses and other details. The statistics for all the results are provided in Supplementary Table 3. The details of the target protein antibodies are provided in Supplementary Table 4.

## RESULTS

### CUS induced depressive-like behaviors in mice and impaired hippocampal synapses in mice

*CUS induced depressive-like behavior in mice*. In the present study, CUS was used to induce depressive-like behaviors in mice.

The timelines of the experiment are shown in Fig. 1A. From the 2nd week to the 4th week, statistically significant differences in body weight were observed between the control group and the CUS group (Supplementary Fig. 2A).

In the SPT, there was no significant difference in sucrose preference between the two groups of mice at the beginning of the experiment. However, after four weeks, the sucrose preference of mice in the CUS group was significantly lower than that of the control group (Fig. 1B).

In the TST, the immobility time of the mice in the CUS group was significantly longer than that of the control group (Fig. 1C). In FST, there was no significant difference in immobility time between the two groups of mice (Supplementary Fig. 2B). These results showed that CUS intervention successfully induced depressive-like behaviors in mice.

*CUS induced synaptic impairment in the hippocampi of mice*. Given that chronic stress can impair synaptic structure, we examined the effects of CUS on dendritic spines, excitatory synapses and inhibitory synapses in the hippocampus.

We used western blotting and immunofluorescence staining to measure the expression levels of MAP2, a protein related to neuronal morphology. The results revealed that the protein levels of MAP2 in the hippocampi of the CUS group were significantly lower than those in the control group (Fig. 1D, E). Moreover, the

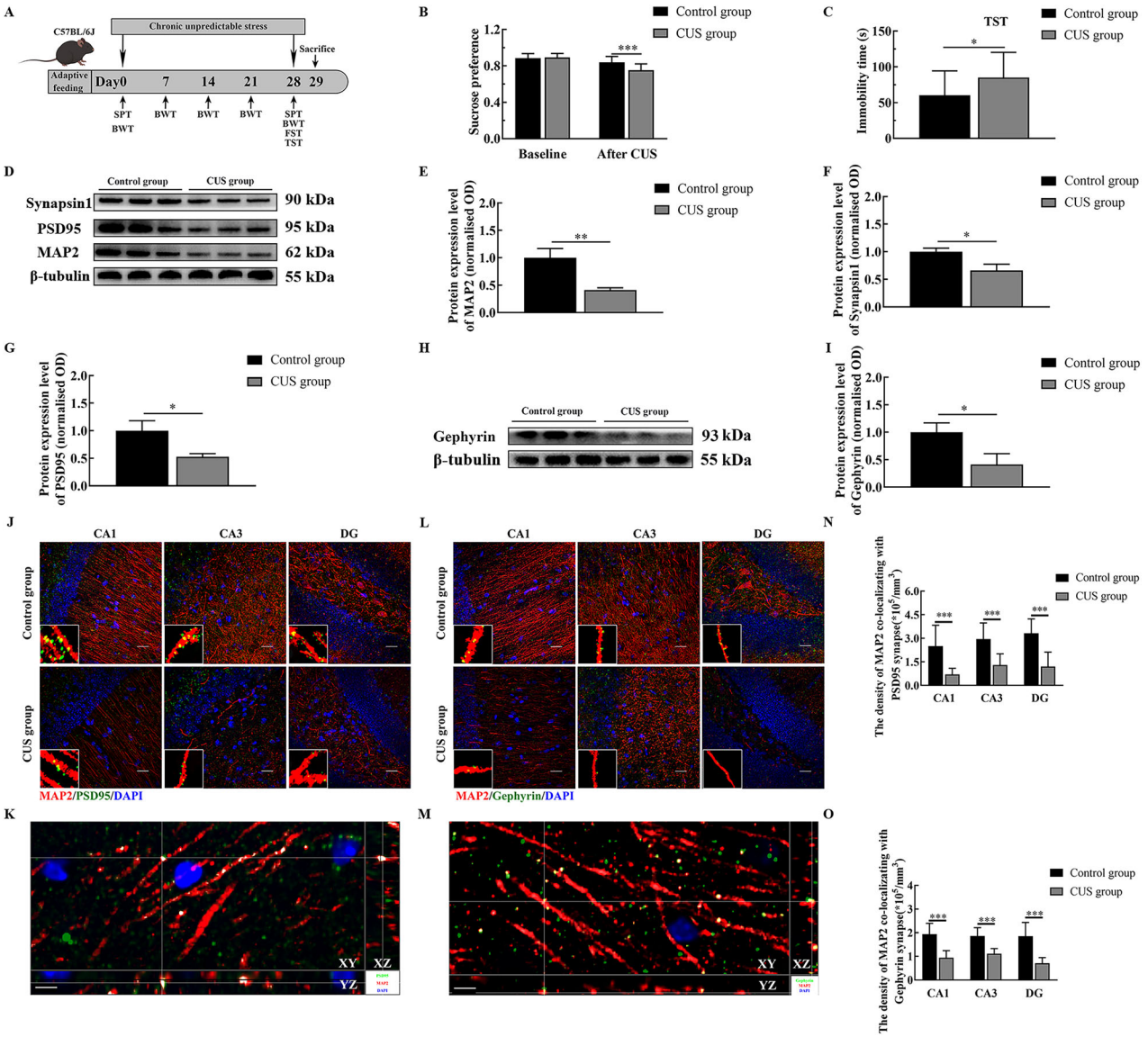


**Fig. 1 CUS induced depressive-like behaviors in mice and impaired hippocampal synapses. A** Schematic of the experimental timeline. The experiment lasted a total of 28 days. SPT: sucrose preference test; BWT: body weight test; FST: forced swimming test; TST: tail suspension test. **B** Sucrose preference of the mice. **C** Immobility times in the TST. **D** Representative western blot images of MAP2, Synapsin1 and PSD95 expression in the hippocampus. **E** MAP2 expression levels in the hippocampus. **F** Synapsin1 expression levels in the hippocampus. **G** PSD95 expression levels in the hippocampus. **H** Representative western blot images of Gephyrin expression in the hippocampus. **I** Gephyrin expression levels in the hippocampus. **J** Representative images of immunofluorescence staining for MAP2 (red), PSD95 (green) and DAPI (blue) in the hippocampus. Scale bar = 50 μm. **K** 3D schematic diagrams of immunofluorescence staining for $MAP2^{+}$/$PSD95^{+}$ (white puncta indicate colocalization). Scale bar = 5 μm. **L** Representative images of immunofluorescence staining for MAP2 (red), Gephyrin (green) and DAPI (blue) in the hippocampus. Scale bar = 50 μm. **M** 3D schematic diagrams of immunofluorescence staining for $MAP2^{+}$/$Gephyrin^{+}$ (white puncta indicate colocalization). Scale bar = 5 μm. **N** Semiquantitative analyses of the intensity of $MAP2^{+}$/$PSD95^{+}$ staining in the CA1, CA3 and DG regions. **O** Semiquantitative analysis of the intensity of $MAP2^{+}$/$Gephyrin^{+}$ staining in the CA1, CA3 and DG regions. The data are shown as the means ± SDs. * indicates significant differences as follows: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

immunofluorescence intensities of MAP2 in three dimensions in each hippocampal region were significantly lower in the CUS group than in the control group (Supplementary Fig. 3A, B).

The levels of presynaptic and postsynaptic membrane markers (synapsin 1 and PSD95) were subsequently measured in the hippocampus. Compared with those in the control group, the protein expression levels of synapsin 1 and PSD95 in the hippocampal tissue of the mice in the CUS group were significantly lower (Fig. 1D, F, G). Moreover, immunofluorescence staining for PSD95 was assessed in three dimensions in the hippocampal regions. As shown in Supplementary Fig. 4A, the density of PSD95 in the hippocampal subregion of the CUS group was significantly lower than that in the control group (Supplementary Fig. 4B).

To further elucidate the impact of CUS intervention on inhibitory synapses, we measured the levels of the inhibitory postsynaptic membrane marker Gephyrin in the hippocampus. The results revealed that the protein levels of Gephyrin in the CUS group were significantly lower than those in the control group (Fig. 1H, I). The immunostaining results further revealed that the protein fluorescence intensities of Gephyrin in the CA1, CA3 and DG regions of the hippocampi in the CUS group were significantly lower than those in the control group (Supplementary Fig. 5A, B).

In addition, we assessed the colocalization of MAP2 with PSD95 or Gephyrin in the tissue. As shown in Fig. 1J–M, the results of the

quantitative immunofluorescence staining revealed that exposure to CUS led to lower fluorescence intensities of $MAP2^+/PSD95^+$ and $MAP2^+/Gephyrin^+$ in the CA1, CA3 and DG regions (Fig. 1N, O). The above results indicate that the number of excitatory and inhibitory synapses on neurons in the hippocampal regions was reduced by CUS intervention.

### CUS decreased the adiponectin mRNA expression levels in adipose tissue, adiponectin protein levels in plasma, and AdipoR1 expression levels in the hippocampus

In the present study, we measured the mRNA expression levels of adiponectin in adipose tissue and plasma adiponectin, as well as the AdipoR expression levels in the hippocampi of mice in the two groups. The ELISA results revealed that the concentrations of total, high-molecular-weight (HMW), medium-molecular-weight (MMW) and low-molecular-weight (LWM) adiponectin in the plasma of the mice were significantly lower in the CUS group than in the control group (Fig. 2A). The results revealed that adiponectin mRNA levels in eWAT were lower in the CUS group than in the control group (Fig. 2B), indicating that CUS could lead to a decrease in adiponectin synthesis.

In addition, both the mRNA and protein levels of hippocampal AdipoR1 were significantly lower in the CUS group than in the control group (Fig. 2C, E, F). In contrast to the decrease in AdipoR1, the hippocampal AdipoR2 mRNA and protein levels were not significantly different between the control group and the CUS group (Fig. 2D, G, H). These data demonstrated that CUS downregulated adiponectin mRNA in adipose tissue, reduced circulating adiponectin levels, suppressed hippocampal AdipoR1 expression, and did not affect AdipoR2 levels.

### Hippocampal AdipoR1 knockdown induced depressive-like behaviors and impaired synaptic plasticity in mice

To investigate the role of the hippocampal adiponectin/AdipoR1 pathway in depressive-like behaviors and synaptic plasticity, we knocked down hippocampal AdipoR1 by stereotactically injecting AAV into the bilateral hippocampi of wild-type mice. The experimental timeline is illustrated in Fig. 3A. Successful bilateral hippocampal AAV delivery was confirmed, as shown in Fig. 3B.

*Knockdown of hippocampal AdipoR1 induced depression-like and passive stress-coping behaviors in mice.* In the present study, there were no significant differences in body weight between the control group and the AdipoR1KD group after AAV injection (Supplementary Fig. 6A).

In the SPT, while both groups presented similar baseline preferences prior to injection, the AdipoR1KD group presented significantly reduced sucrose preference compared with the control group at 4 weeks post-injection (Fig. 3C).

At the 4-week post-injection time point, AdipoR1KD mice displayed significantly prolonged immobility times in the FST compared with those in the control group (Fig. 3D), whereas no group differences were detected in the TST (Supplementary Fig. 6B). These findings suggest that hippocampal AdipoR1 knockdown promotes depression-like phenotypes and passive stress-coping-like behaviors in mice.

*Knockdown of hippocampal AdipoR1 did not affect the expression levels of hippocampal AdipoR2 or adiponectin in plasma, eWAT or CSF.* As shown in Fig. 3E–J, both the mRNA and protein expression levels of hippocampal AdipoR1 were significantly lower in the AdipoR1KD group than in the control group, whereas AdipoR2 expression remained unchanged. To determine whether hippocampal AdipoR1 downregulation affects adiponectin signaling, we analyzed adiponectin levels in eWAT, plasma and CSF. No significant differences in adiponectin mRNA levels were detected in the eWAT (Fig. 3K). No significant differences in total or multimeric (HMW, MMW and LWM) adiponectin concentrations were detected in the plasma or CSF (Fig. 3L–M). These results demonstrated that hippocampal AdipoR1 knockdown specifically reduced AdipoR1 expression without altering AdipoR2 levels or affecting systemic adiponectin production and distribution.

*Knockdown of hippocampal AdipoR1 induced synaptic impairment in the hippocampi of mice.* Stereological analyses revealed significantly fewer spinophilin-immunoreactive puncta in the CA1 and DG regions of AdipoR1KD mice than in those of controls (Fig. 4A,B). However, there was no significant difference in the total number of spinophilin-immunoreactive puncta in the CA3 region between the two groups (Fig. 4A,B).

We next assessed hippocampal MAP2 expression using western blotting and immunofluorescence. Western blot analyses revealed significantly lower MAP2 protein levels in AdipoR1KD mice than in control mice (Fig. 4C, D). Immunofluorescence revealed reduced MAP2 intensity in three dimensions in the CA1 region of AdipoR1KD mice, whereas the CA3 and DG regions were not significantly different (Supplementary Fig. 7A, B).

To investigate whether knockdown of hippocampal AdipoR1 affects synapse formation, we quantified the synaptic markers synapsin 1 and PSD95. Western blot analyses revealed significantly reduced membrane protein expression of both markers in AdipoR1KD hippocampal tissue (Fig. 4E, F). Three-dimensional immunofluorescence analysis further demonstrated decreased PSD95 density in all the hippocampal subregions (CA1, CA3, and DG) of AdipoR1KD mice (Supplementary Fig. 8A, B).

To evaluate the effects of the knockdown on inhibitory synapses, we analyzed hippocampal Gephyrin expression. Western blotting revealed significantly lower Gephyrin protein levels in AdipoR1KD mice than in control mice (Fig. 4G, H). Immunostaining confirmed decreased Gephyrin intensity in the CA1 and DG regions, whereas the intensity in CA3 was not significantly different (Supplementary Fig. 9A, B).

We next assessed the colocalization of MAP2 with PSD95 or Gephyrin in the hippocampal subregions (Fig. 4I–L). The results of quantitative immunofluorescence staining revealed that hippocampal AdipoR1 knockdown led to a lower fluorescence density of $MAP2^+/PSD95^+$ and $MAP2^+/Gephyrin^+$ in the CA1, CA3 and DG regions in the AdipoR1KD group than in the control group (Fig. 4M, N).

These results indicate that the number of excitatory and inhibitory synapses on neurons in the hippocampal regions was reduced by knockdown of hippocampal AdipoR1.

## DISCUSSION

Previous studies have indicated that impaired synaptic plasticity is a key pathological change in depression [34], but the mechanism underlying this pathological change has not been clarified. Recent clinical evidence has suggested a strong association between adiponectin and depressive symptoms in depressive disorder patients [35]. However, it is unclear whether impaired synaptic plasticity in depression is related to changes in adiponectin/AdipoR signaling. The present study has three key findings: 1. CUS induced hippocampal synaptic structural impairments and reduced expression of synapse-related proteins, which correlated with the suppression of adiponectin/AdipoR1 (but not AdipoR2) signaling. 2. Hippocampal AdipoR1 knockdown recapitulated the behavioral features of depression, including a reduction in the percentage of sucrose preference and the presence of passive stress-coping-like behaviors. 3. AdipoR1 deficiency led to significant synaptic deficits, mainly manifested as a reduced number of dendritic spines and a decreased density of excitatory/inhibitory synapses in hippocampal neurons. These findings provide a possible mechanistic explanation for the synaptic impairment observed in depression.

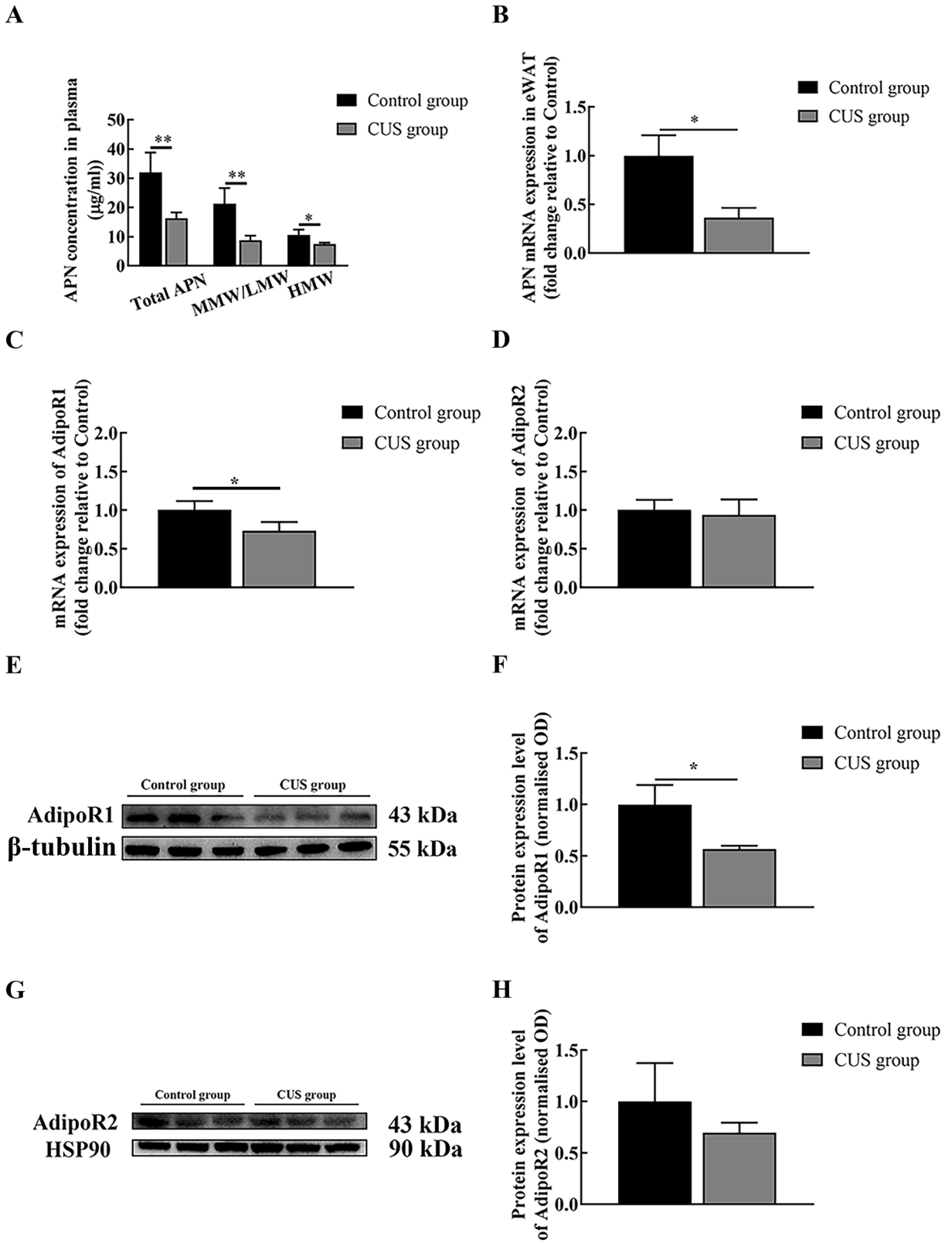


**Fig. 2 CUS decreases adiponectin/AdipoR1 signaling in the hippocampus. A** ELISA results showing the concentrations of total, HMW, MMW and LMW adiponectin in the plasma. **B** Relative levels of adiponectin mRNA in eWAT. **C** Relative levels of AdipoR1 mRNA in the hippocampus. **D** Relative levels of AdipoR2 mRNA in the hippocampus. **E** Representative western blot images of AdipoR1 expression in the hippocampus. **F** AdipoR1 expression levels in the hippocampus. **G** Representative western blot images of AdipoR2 expression in the hippocampus. **H** AdipoR2 expression levels in the hippocampus. The data are shown as the means ± SDs. * indicates significant differences as follows: $^{*}P < 0.05$ and $^{**}P < 0.01$.

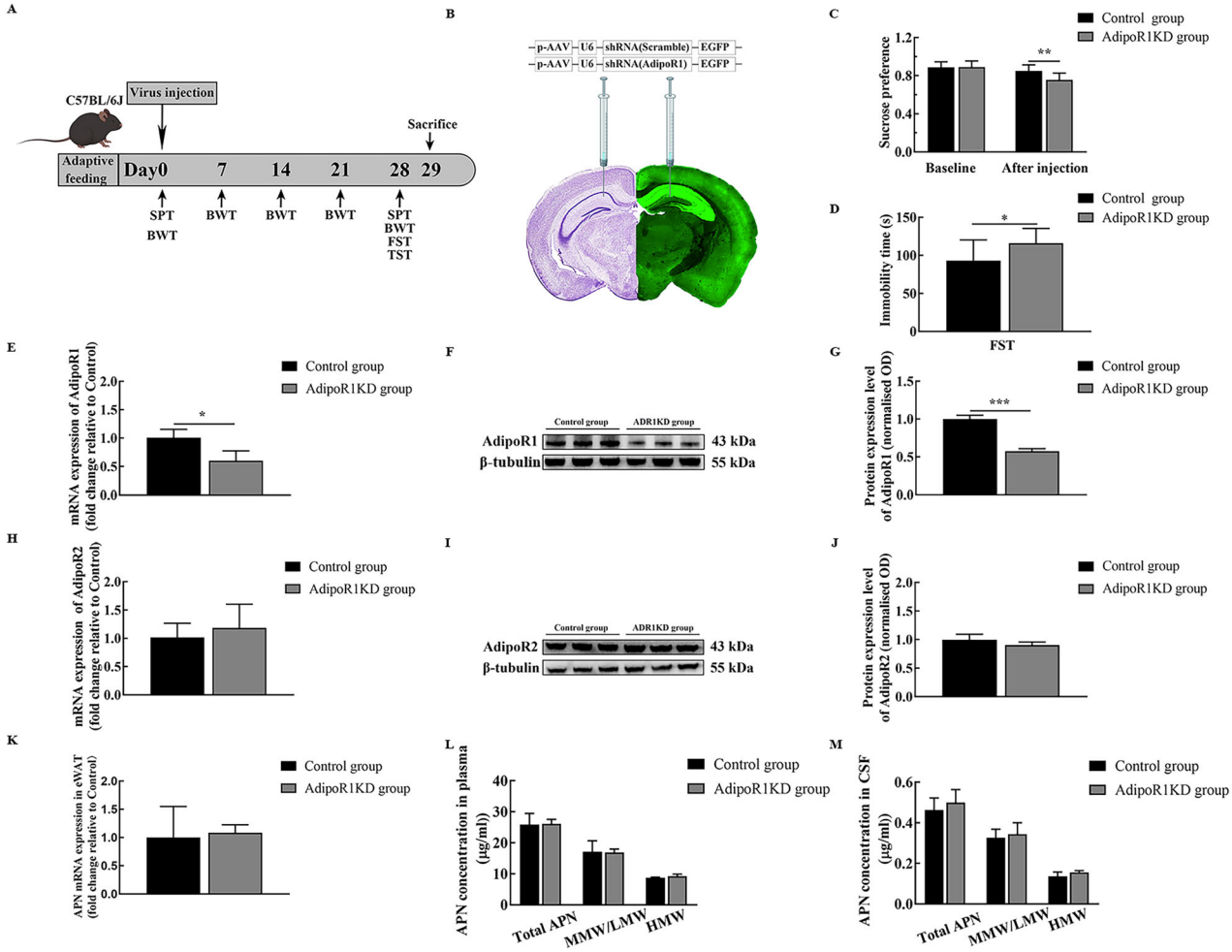


**Fig. 3 A reduction in the expression of AdipoR1 in the hippocampus induces depressive behaviors. A** Schematic of the experimental timeline. The experiment lasted a total of 28 days. **B** Representative immunofluorescence image of virus expression. **C** Sucrose preference of the mice. **D** Immobility times in the FST. **E** Relative levels of AdipoR1 mRNA in the hippocampus. **F** Representative western blot images of AdipoR1 expression in the hippocampus. **G** AdipoR1 expression levels in the hippocampus. **H** Relative levels of AdipoR2 mRNA in the hippocampus. **I** Representative western blot images of AdipoR2 expression in the hippocampus. **J** AdipoR2 expression levels in the hippocampus. **K** Relative levels of adiponectin mRNA in eWAT. **L** ELISA results showing the concentrations of total, HMW, MMW and LMW adiponectin in the plasma. **M** ELISA results showing the concentrations of total, HMW, MMW and LMW adiponectin in the CSF. The data are shown as the means ± SDs. * indicates significant differences as follows: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

Synaptic defects in the hippocampus are important pathological changes associated with depression, and stress is a risk factor for depression [36, 37]. Numerous studies have shown that stress induces dendritic atrophy, a decrease in the number of synapses and synaptic dysfunction in the hippocampus. Dendritic spines constitute mainly postsynaptic components, including spinophilin (Sp), which is expressed on the dendritic spinous membrane and is expressed in more than 90% of excitatory synapses [38–40]. Our previous study revealed that CUS model mice presented with fewer $Sp^{+}$ dendritic spines representing excitatory synapses in the CA1, CA3 and DG regions of the hippocampus, suggesting that the synaptic structure is damaged in depression [41]. In addition, the protein synapsin Ia/b reversibly tethers synaptic vesicles to the cytoskeleton of the presynaptic terminal to modulate neurotransmitter release [42]. In patients with depression, microarray gene profiling studies have revealed lower expression of synapsin Ia/b genes in the dlPFC, corresponding to a lower number of synapses [13, 43]. Our current data indicated that CUS intervention significantly decreased synapsin Ia/b protein levels in the hippocampus of mice. PSD95 is an excitatory postsynaptic membrane protein that binds to synapse-associated receptors and the cytoskeleton to drive glutamatergic synaptic maturation, which in turn affects the number and size of dendritic spines and synaptic function [11, 44, 45]. In the present study, we found that PSD95 protein levels in the hippocampus and the density of PSD95 puncta in the CA1, CA3 and DG regions of the hippocampus, as evaluated by immunofluorescence staining, were significantly decreased after CUS intervention. In addition, MAP2, a member of the MAP family, is a reliable dendritic marker that regulates the stability of tubulin and plays an important role in maintaining neuronal morphology, neurite outgrowth, and synapse formation [46–48]. During neuronal growth and development, PSD95 is initially located in neuronal cell bodies and is ultimately trafficked to the postsynaptic region of excitatory synapses on dendrites marked by MAP2 [49, 50]. In this study, we double-labeled MAP2 and PSD95 via immunofluorescence staining to assess the density of MAP2-PSD95 double-stained puncta, which revealed that the PSD95 protein was expressed on dendrites. The results also revealed that CUS intervention significantly decreased the density of MAP2-PSD95 double-stained puncta in the CA1, CA3 and DG regions of the hippocampus in mice, which indicates that the number of functional excitatory synapses on mature neurons was reduced. Compared with the evidence obtained from the measurement of the expression levels

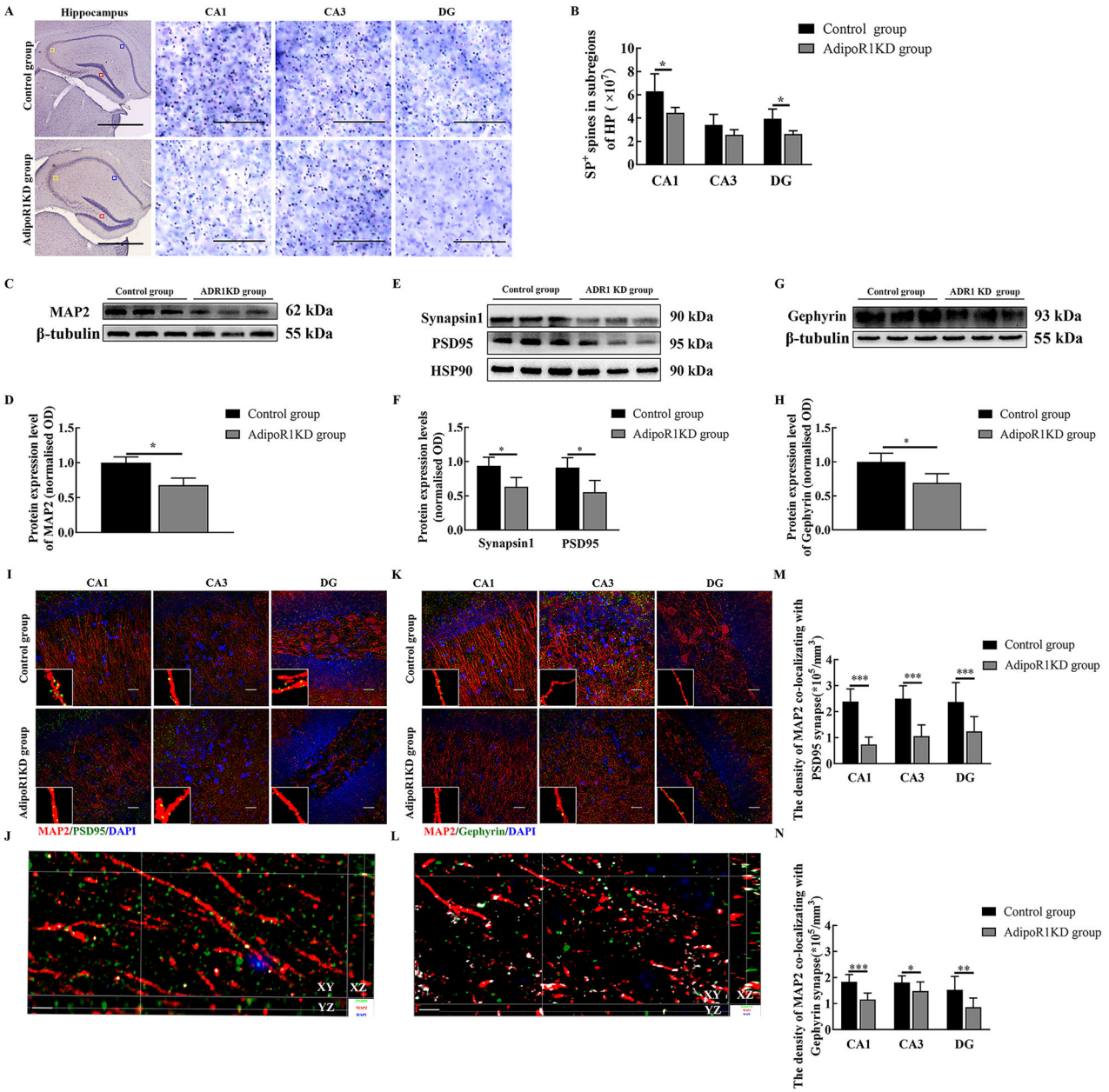


**Fig. 4 A reduction in the expression of AdipoR1 in the hippocampus induces the synaptic impairment in the hippocampus.** **A** Representative immunohistochemical image of dendritic spines. The area covered by the blue square represents the CA1 region, the area covered by the yellow square represents the CA3 region, and the area covered by the red square represents the DG region. Scale bar (two pictures on the top left and bottom left) = 1 mm. Scale bar (six pictures on the upper right and lower right) = 40 μm. **B** Number of dendritic spines in the hippocampal subregions. **C** Representative western blot images of MAP2 expression in the hippocampus. **D** MAP2 expression levels in the hippocampus. **E** Representative western blot images of Synapsin1 and PSD95 expression in the hippocampus. **F** Synapsin1 and PSD95 expression levels in the hippocampus. **G** Representative western blot images of Gephyrin expression in the hippocampus. **H** Gephyrin expression levels in the hippocampus. **I** Representative images of immunofluorescence staining for MAP2 (red), PSD95 (green) and DAPI (blue) in the hippocampus. Scale bar = 50 μm. **J** 3D schematic diagrams of immunofluorescence staining for $MAP2^{+}/PSD95^{+}$ (white puncta indicate colocalization). Scale bar = 5 μm. **K** Representative images of immunofluorescence staining for MAP2 (red), Gephyrin (green) and DAPI (blue) in the hippocampus. Scale bar = 50 μm. **L** 3D schematic diagrams of immunofluorescence staining for $MAP2^{+}/Gephyrin^{+}$ (white puncta indicate colocalization). Scale bar = 5 μm. **M** Semiquantitative analysis of the intensity of $MAP2^{+}/PSD95^{+}$ staining in the CA1, CA3 and DG regions. **N** Semiquantitative analyses of the intensity of $MAP2^{+}/Gephyrin^{+}$ in the CA1, CA3 and DG regions. The data are shown as the means ± SDs. * indicates significant differences as follows: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

of synaptic plasticity-related proteins, the immunofluorescence results intuitively revealed that CUS caused functional excitatory synaptic defects in subregions of the hippocampus [43]. Moreover, accumulating evidence has suggested that GABA receptor expression is highly altered in depression [51–54]. Kolata et al. reported that hippocampal GABA levels were reduced by approximately 50% in GAD67 knockout mice, which also exhibited depressive-like behaviors, suggesting that hippocampal GABA regulation is involved in the pathology of depression [55]. Gephyrin is a postsynaptic scaffold anchoring GABA and glycine receptors to form inhibitory synapses, which participate in the regulation of inhibitory neurotransmission [56]. In the present

study, Gephyrin protein levels, Gephyrin-stained puncta density and MAP2-Gephyrin double-stained puncta density were decreased in the CA1, CA3 and DG regions of the hippocampus after CUS intervention. Although the amplitude and frequency of inhibitory postsynaptic currents are commonly used to reflect inhibitory GABA inputs in electrophysiology analysis [57], our data provide sufficient morphological evidence of a decreased density of functional inhibitory synapses in the hippocampus under chronic stress conditions. Specifically, our morphological results indicate that CUS intervention can cause structural and functional impairments in both excitatory and inhibitory synapses in the hippocampus.

Importantly, the CUS intervention induced depressive-like symptoms by impairing synaptic structure and function. However, the mechanism underlying this pathological change has not been clarified. Adiponectin is an adipocyte-secreted hormone whose pathophysiological roles in depression have previously been demonstrated [58–60]. Adiponectin is synthesized mainly from peripheral adipose tissue and then secreted into the blood [61]. In the present study, we measured the levels of adiponectin mRNA in eWAT and the plasma concentrations of different forms of adiponectin after CUS intervention. Our findings indicated that CUS intervention significantly decreased the mRNA level of adiponectin in eWAT and the concentration of adiponectin in the plasma of the mice. Thus, it seems reasonable to speculate that the decrease in adiponectin levels may be attributed to a depression-like behavioral phenotype. Evidence from animal studies has indicated that adiponectin can pass through the blood–brain barrier to exert its effects on the brain, including regulating synaptic plasticity, by binding to AdipoRs [28, 62]. However, previous studies have been unable to clarify which adiponectin receptor changes are involved in the regulation of synaptic plasticity in depression [59]. In our study, we measured the expression levels of AdipoRs in the hippocampi of mice and found that CUS intervention significantly decreased the levels of AdipoR1 mRNA and protein but not those of AdipoR2 in the hippocampi of the mice. AdipoR1 is a major adiponectin receptor in the central nervous system and may play an important role in mediating adiponectin-dependent functions involved in regulating depressive-like behaviors and the pathology of depression [63–65]. Shah et al. revealed that osmotin treatment could modulate the AdipoR1/AMPK/SIRT1 pathway to improve presynaptic and postsynaptic dysfunction in Alzheimer's disease [66]. On this basis, we propose that alterations in AdipoR1 expression in the hippocampus may be involved in the regulation of synaptic impairment in depression.

In the present study, hippocampal AdipoR1 was knocked down in mice via the injection of an AAV. Our results indicated that this injection significantly decreased the levels of AdipoR1 mRNA and protein but did not affect the concentrations of adiponectin in the plasma or CSF or the levels of AdipoR2 mRNA and protein in the hippocampus. Behavioral tests revealed that hippocampal AdipoR1 knockdown significantly induced anhedonic behaviors. Moreover, in the FST, the immobility time of the mice in the AdipoR1-KD group was clearly greater than that of the control group, whereas the immobility time in the TST did not differ between the two groups. Traditionally, the SPT has been employed to evaluate the effects of anhedonia on rodents [67]. The FST has been reported to be more relevant for evaluating stress-coping strategies, primarily because of its predictive validity for the effects of certain drugs [68]. The TST has great utility in assessing antidepressant-related and despair-like behaviors [69]. Although there was no significant difference in the results of the TST, the results of the SPT and FST demonstrated that a decrease in the expression of AdipoR1 in the hippocampus could result in anhedonic behaviors and passive stress-coping behaviors. We speculate that knockdown of hippocampal AdipoR1 could prevent adiponectin from binding effectively to its corresponding receptors and subsequently induce depressive-like behaviors.

To verify the role of hippocampal AdipoR1 in synaptic function and structure, immunohistochemistry was combined with stereological technology to accurately quantify the number of dendritic spines in the hippocampi of hippocampal AdipoR1-knockdown mice. Our stereological results revealed that knockdown of hippocampal AdipoR1 significantly decreased the number of $SP^+$ dendritic spines in the CA1 and DG regions but not in the CA3 region of the hippocampus, indicating a relationship between alterations in hippocampal AdipoR1 and synaptic defects. In addition, we assessed many other synaptic indicators to explore changes in excitatory and inhibitory synapses in the hippocampi of mice after hippocampal AdipoR1 knockdown. These results indicated that reducing the expression of hippocampal AdipoR1 decreased the expression of synaptic-related functional proteins (synapsin 1, PSD95, MAP2 and Gephyrin) and the density of fluorescence-stained puncta (PSD95, MAP2-PSD95 and MAP2-Gephyrin puncta) in the CA1, CA3 and DG regions of the hippocampus, whereas the density of Gephyrin-stained puncta decreased only in the CA1 and CA3 regions. Importantly, Weisz et al. reported decreased levels of synaptic proteins (PSD95 and SNAP25) in adiponectin knockout (APN-KO) mice, but further studies examining the role of specific AdipoRs in synaptic processes are lacking [70]. To better understand the role of AdipoR1 in hippocampal synaptic function, we first observed that AdipoR1 affects the number of dendritic spines in the hippocampus with an unbiased stereological method [71]. Our results provide the first evidence that a reduction in the expression of hippocampal AdipoR1 might directly impair excitatory and inhibitory synaptic functions and structures. Notably, hippocampal AdipoR1 knockdown disrupted synaptic plasticity mainly in the CA1 and DG regions of the hippocampus. Previous studies have shown that the key consequences of stress exposure in the hippocampus are the suppression of neurogenesis in the DG and dendritic remodeling in the CA, particularly in the CA1 subfield [72, 73], in which pyramidal neurons of the CA3 regions, known to drive CA1 spatial representations, show pronounced dendritic retraction in response to chronic stress [74, 75]. This may explain the significant impairments in the CA1 and DG regions but not the CA3 region following hippocampal AdipoR1 knockdown, but this hypothesis needs to be further verified. Thus, we found that downregulation of hippocampal AdipoR1 expression mainly induced dysfunction in synaptic plasticity in the CA1 and DG regions of the hippocampus. What is the possible mechanism underlying this relationship? AdipoR1 is abundantly expressed in both presynaptic and postsynaptic compartments in the hippocampal synaptosome [31]. It has been reported that activation of AdipoR1 can activate AMPK signaling, which plays a key role in maintaining the synaptic energy supply to sustain synaptic activity in the brain [76, 77]. Therefore, one possible reason for the apparent synaptic defects in the hippocampus of AdipoR1-knockdown mice is that downregulating hippocampal AdipoR1 expression may induce the AMPK-mediated energy deficits associated with synaptic dysfunction. However, whether AdipoR1 regulates synapses by influencing AMPK signaling is unclear and needs to be further studied.

Taken together, our findings indicate that downregulating hippocampal AdipoR1 expression induces hippocampal synaptic damage, which might be an important mechanism underlying the occurrence and development of depression. Drugs or other intervention methods targeting AdipoR1 may be developed in the future to reverse synaptic damage in the brains of patients with depression and thereby improve symptoms of depression.

## DATA AVAILABILITY

The authors declare that data supporting the findings of this study are available from the corresponding author upon request.

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## AUTHOR CONTRIBUTIONS

Peilin Zhu: Article writing, project administration, formal analysis, data curation, and conceptualization. Yanmin Luo: Methodology, project administration, funding acquisition, formal analysis, data curation, and conceptualization. Yue Li: Methodology, project administration, formal analysis, and data curation. Jing Tang: Methodology and Funding acquisition. Li Liu: Methodology. Yuhui Deng: Animal experimental operation. Jing Li: Animal experimental operation. Lin Jiang: Animal experimental operation. Wenyu Yang: Animal experimental operation. Qian Xiao: Methodology. Shun Wang: Methodology. Yuning Zhou: Methodology. Fenglei Chao: Methodology. Lei Zhang: Methodology. Chunni Zhou: Methodology. Xin Liang: Writing - review & editing, supervision, methodology, project administration, and conceptualization. Yong Tang: Writing - review & editing, supervision, resources, project administration, funding acquisition, and conceptualization.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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