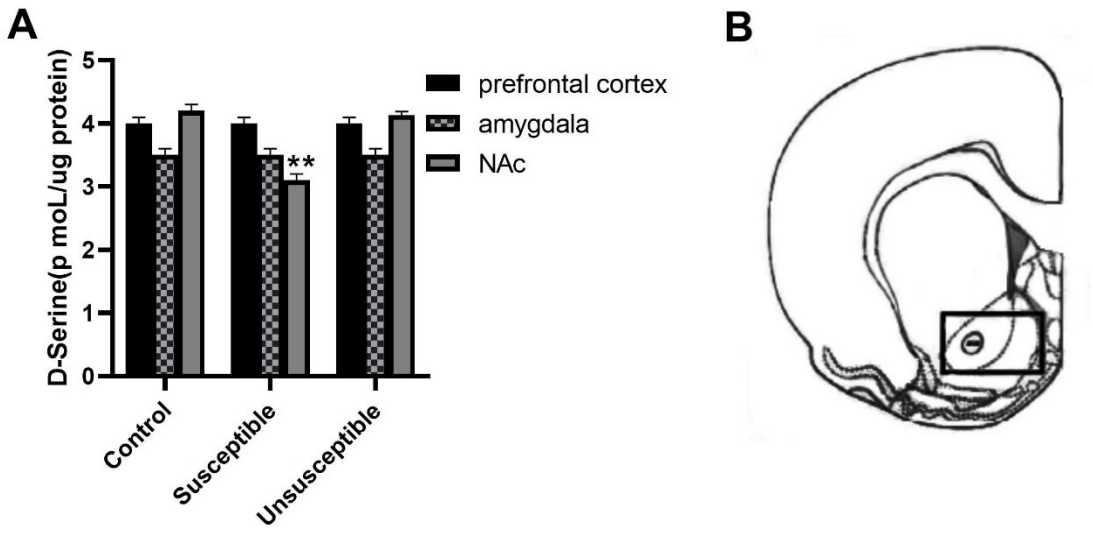

Figure 1 The results of high performance liquid chromatography showed that the concentration of D-serine in NAc was decreased in depression susceptible group.

(A) An average content of D-serine in prefrontal cortex, amygdala and NAc in control group, depression susceptible group and depression unsusceptible group.

(B) Anatomical location of NAc.

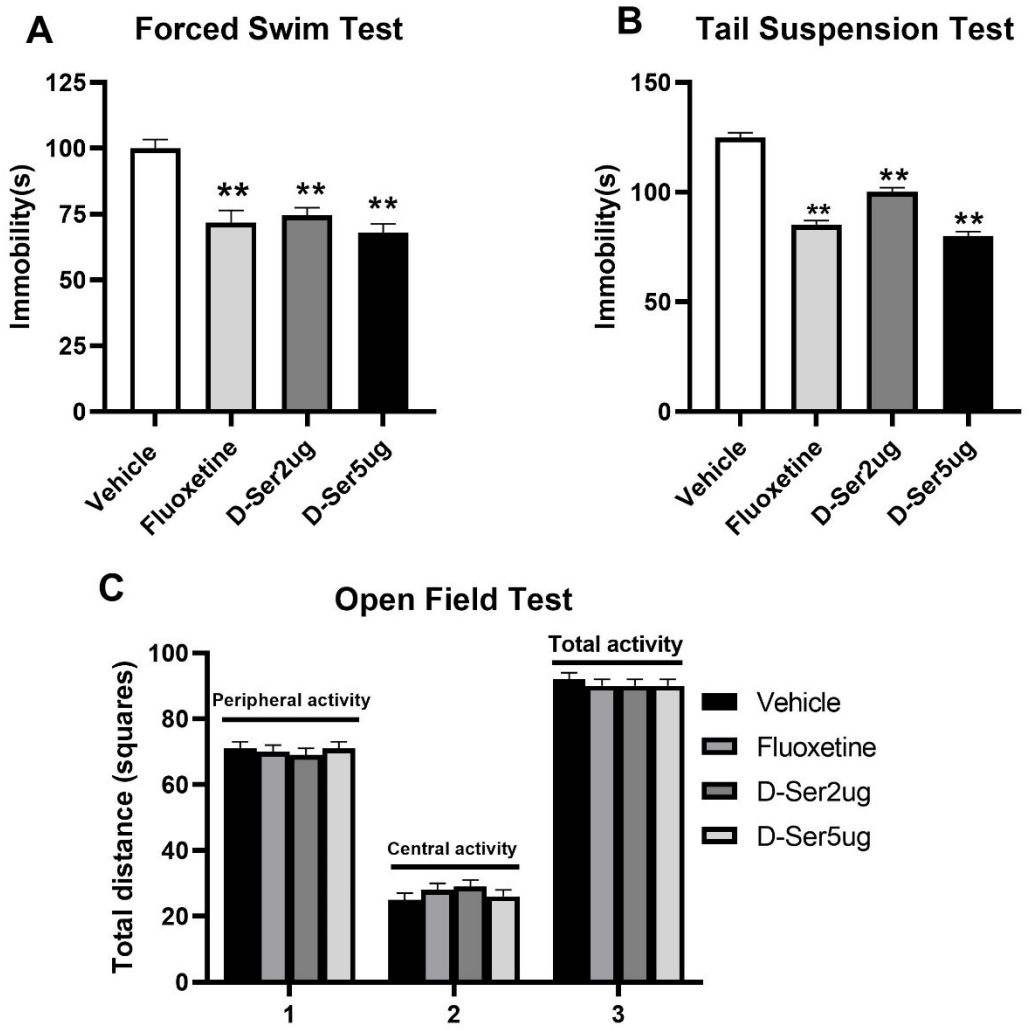

Figure 2 D-serine has antidepressant-like effects in the FST and TST. C57BL/6J mice were injected into the bilateral NAc with a single dose of vehicle (Control), fluoxetine (5 ug/perside), or D-serine (2, 5 ug/perside). The behavioral tests were conducted 30 min after the injection. The vehicle referred to 0.9% saline (injected into the bilateral NAc). (A) D-serine observably reduced the immobility time of C57BL/6J mice in the FST. (B)D-serine observably reduced the immobility time of C57BL/6J mice in the TST. (C)D-serine administration had no effects on the spontaneous locomotor activity of mice in the open-field test. Fluoxetine was used as a positive control. The data are expressed as mean±SEM(n = 12); **P < 0.01, significantly different from control. Comparisons were made by one-way ANOVA followed by post hoc LSD test.

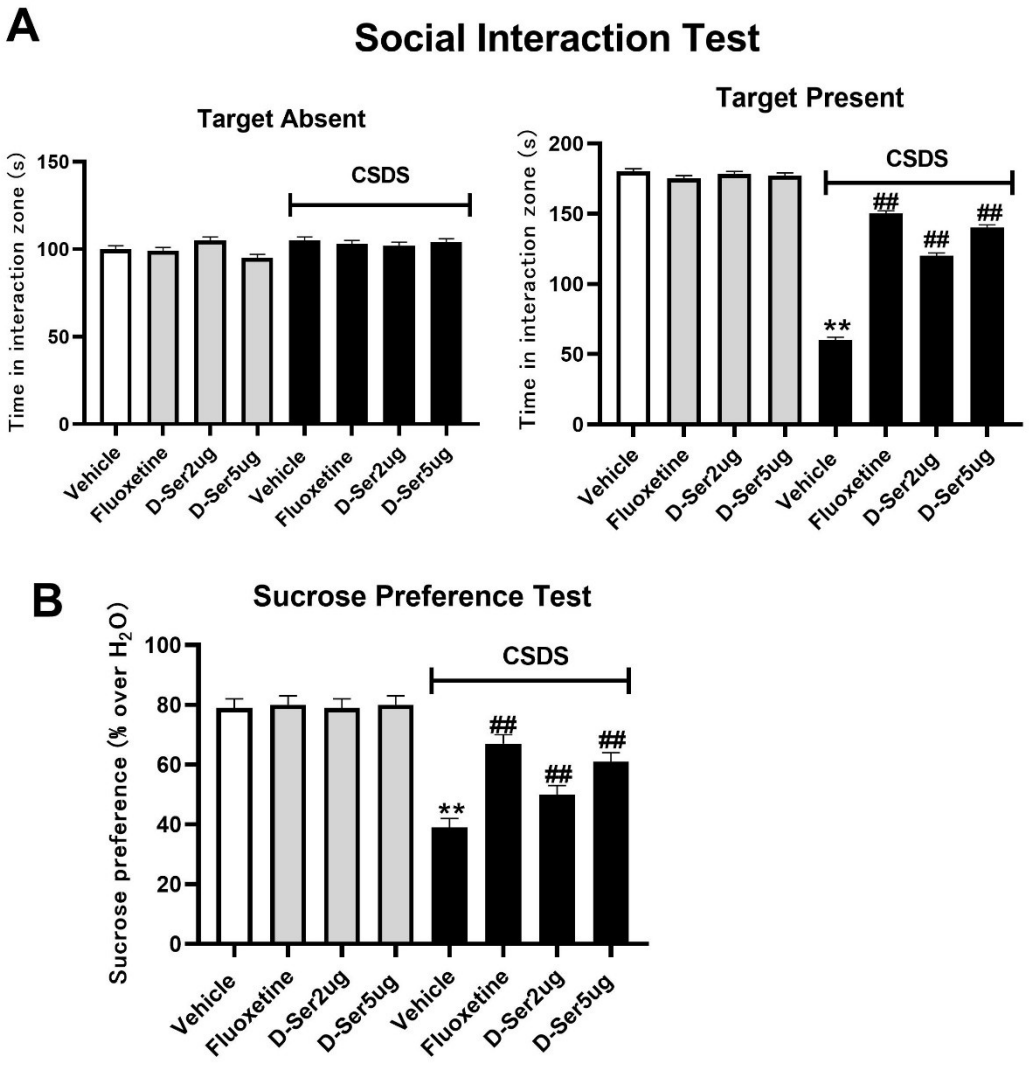

Figure 3 D-serine has antidepressant-like effects in the CSDS model. CSDS-stressed mice received daily injections (injected into the bilateral NAc) of vehicle (Control), fluoxetine (5 ug/perside), or D-serine (2, 5 ug/perside) for 14 days, behavioral tests were then conducted. The vehicle refers to 0.9% saline (injected into the bilateral NAc). (A) The antidepressant-like outcomes of D-serine in the social interaction test. CSDS + D-serine mice spent significantly more time concerned with social interaction than CSDS + vehicle mice. (B) The antidepressant-like outcomes of D-serine in the sucrose preference test. CSDS + D-serine mice showed significantly higher sucrose preference than CSDS + vehicle mice. Data are expressed as means ± SEM (n = 12); **P < 0.01. Comparisons were made by two-way ANOVA followed by post hoc Bonferroni ' s test.

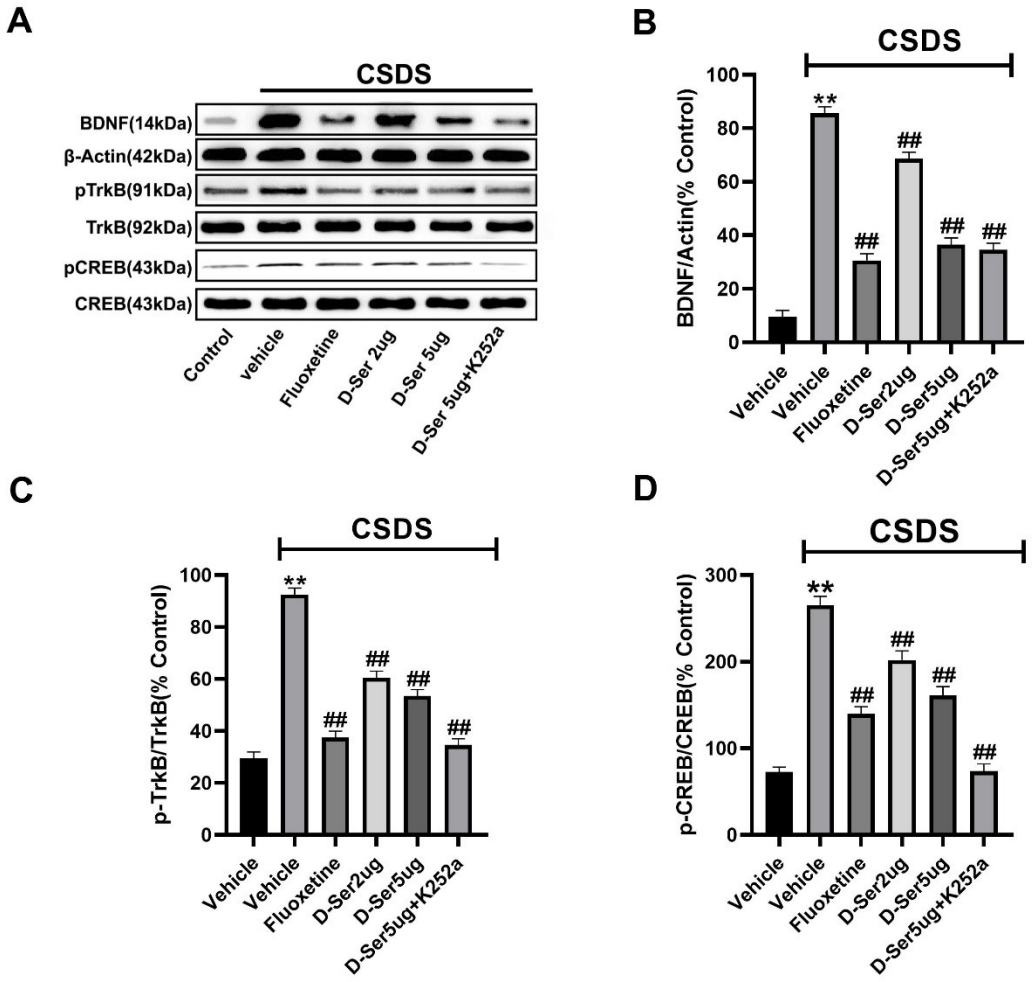

Figure 4 D-serine administration reverses the CSDS-induced increase in the NAc BDNF signaling pathway. Moreover, K252a improves the effects of D-serine on the NAc BDNF signaling pathway. (A) Typical images of our western blotting results. (B. C and D) Our western blotting data displayed that D-serine administration reversed the CSDS-induced increase of NAc BDNF, pTrkB and pCREB protein levels. CSDS + D-serine mice showed meaningfully lower expression of BDNF, pTrkB and pCREB in the NAc than CSDS + vehicle mice. Furthermore, K252a improved the D-serine-induced weakness of NAc BDNF, pTrkB and pCREB expression, as CSDS + D-serine + K252a mice displayed significantly lower BDNF, pTrkB and pCREB levels in the NAc than CSDS + D-serine mice. Data are expressed as means±SEM (n = 5);**P < 0.01, significantly different from control; ##P < 0.01, significantly different from CSDS + vehicle group. Comparisons were made by two-way ANOVA followed by post hoc Bonferroni ' s test.

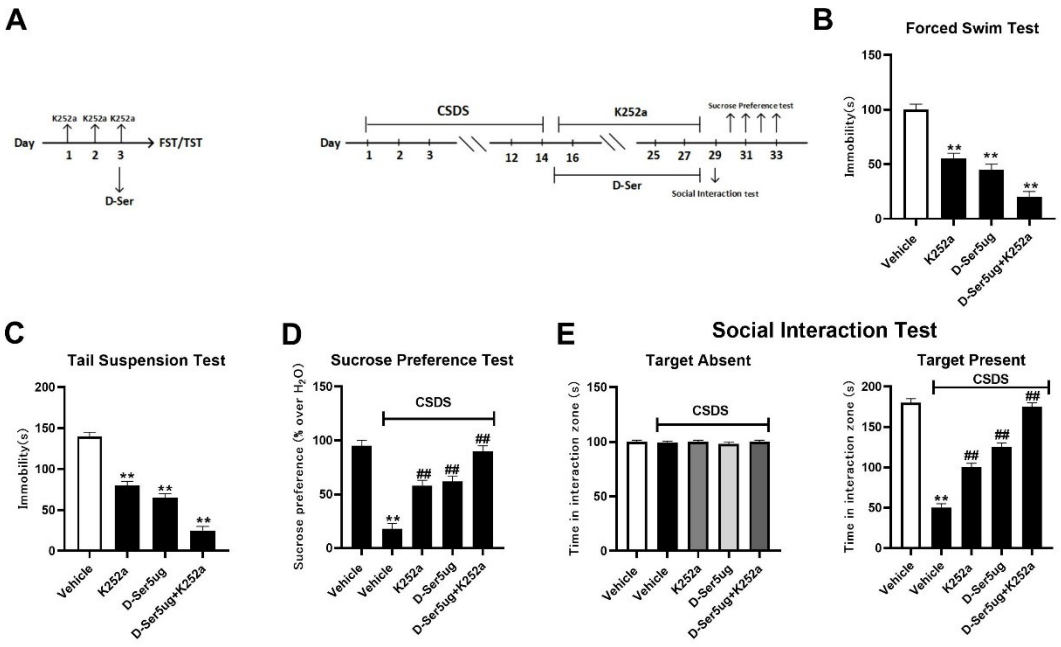

Figure 5 Retardant of the BDNF signaling cascade by K252a infusion enhances the antidepressant effects of D-serine. The vehicle refers to 0.9% saline (injected into the bilateral NAc). (A) Schematic timeline of the experimental steps. A total of 110 C57BL/6J mice were used in this experiment with 144 CSDS-stressed mice and 132 unstressed mice. After 10 days of CSDS, CSDS-susceptible mice received daily injection of D-serine (2, 5 ug/perside) and K252a for another 14 days, after which behavioral tests were performed. (B) Pre-infusion of K252a significantly enhanced the D-serine-induced reduction in immobility in the FST. (C) Pre-infusion of K252a also enhanced the D-serine-induced reduction in immobility in the TST. (D) CSDS + D-serine + K252a mice showed significantly higher sucrose preference than CSDS +D-serine mice. (E) Co-treatment of D-serine with K252a also enhanced the antidepressant effects of D-serine in the social interaction test. CSDS + D-serine + K252a mice showed significantly higher social interaction than CSDS + D-serine mice. Consequences are expressed as means ± SEM (n = 12), **P<0.01 vs control; ##P<0.01 vs CSDS + vehicle. Comparisons were made by two-way ANOVA followed by post hoc Bonferroni ' s test.

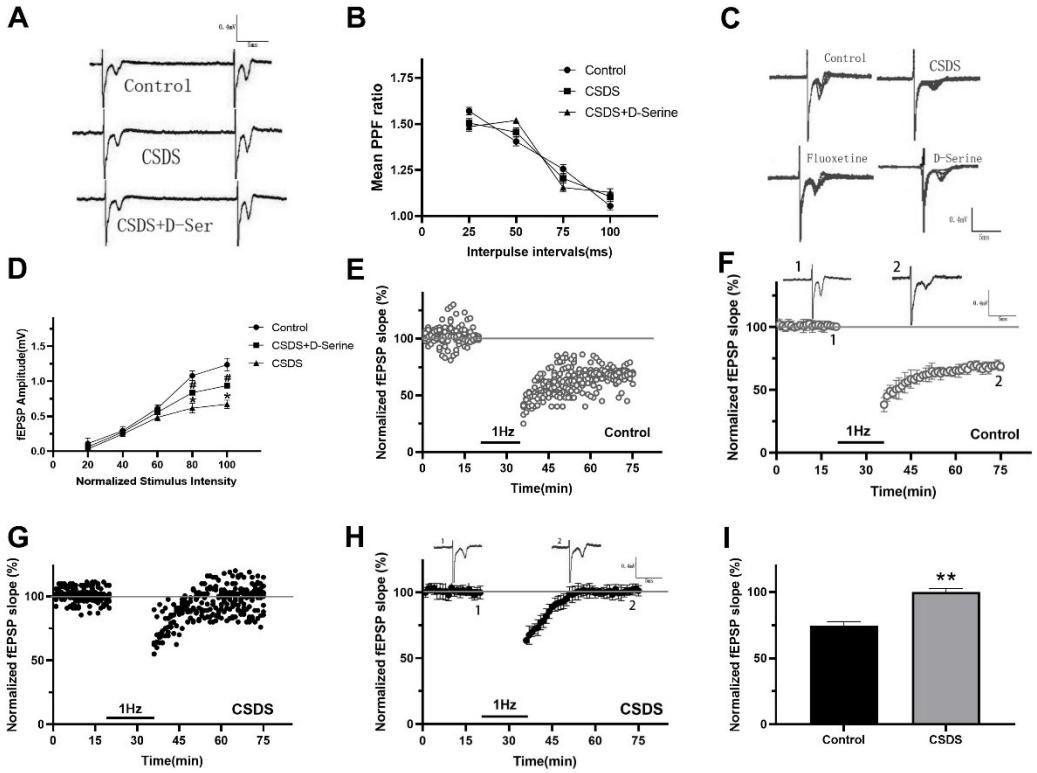

Figure 6.1 NMDAR-LTD of prefrontal cortex-accumbal glutamatergic synapse was disrupted in CSDS mice. (A) Prefrontal cortex-accumbal field potential recordings of acute NAc slices reveal the representative field excitatory postsynaptic potentials (fEPSPs) demonstrated respective recordings from sample experiments at 50 msec inter-pulse interval. (B) Paired-pulse facilitation (PPF) was recorded by changing the intervals between pairs of salts. Paired-pulse ratios, that is to say, slope of fEPSPs no. 2/slope fEPSPs no. 1 were alike among control, CSDS and D-serine treated slices (n = 8). (C) Prefrontal cortex- accumbal field potential recordings of acute brain slices exhibit the characteristic superposed fEPSPs by adding stimulation intensity. (D) Input-output curves illustrating the correlation between the magnitudes of stimulation and evoked reaction for fEPSPs recorded from slices of control and CSDS mice. The CSDS decreased fEPSPs in NAc significantly, compared with control mice (n = 8). The D-serine treated slices increased fEPSPs in NAc significantly, compared with CSDS mice (n = 8). (E) Individual experiment traces showed that LTD was induced in control slices by low-frequency stimulation (LFS). The LFS consisting of a 1-Hz, 900-pulse train, which method has been used to cause NMDAR-LTD in prefrontal cortex-NAc synapse. (F) Averaged data demonstrated that LTD was induced in control slices by LFS. (G) Individual experiment traces showed that LTD was induced in CSDS slices by LFS. (H) Averaged data showed that LTD was induced in CSDS slices by LFS. (I) The column diagram demonstrated the level of LTD 40 minutes after LFS from control mice and CSDS mice. The NMDAR-LTD was impaired in CSDS mice compared with control mice. **p <0 .01 vs. control group. The superimposed fEPSP in the upper portion are recording from representative experiments taken at the time indicated by the number. Each point was the normalized mean ± SEM of eight slices.

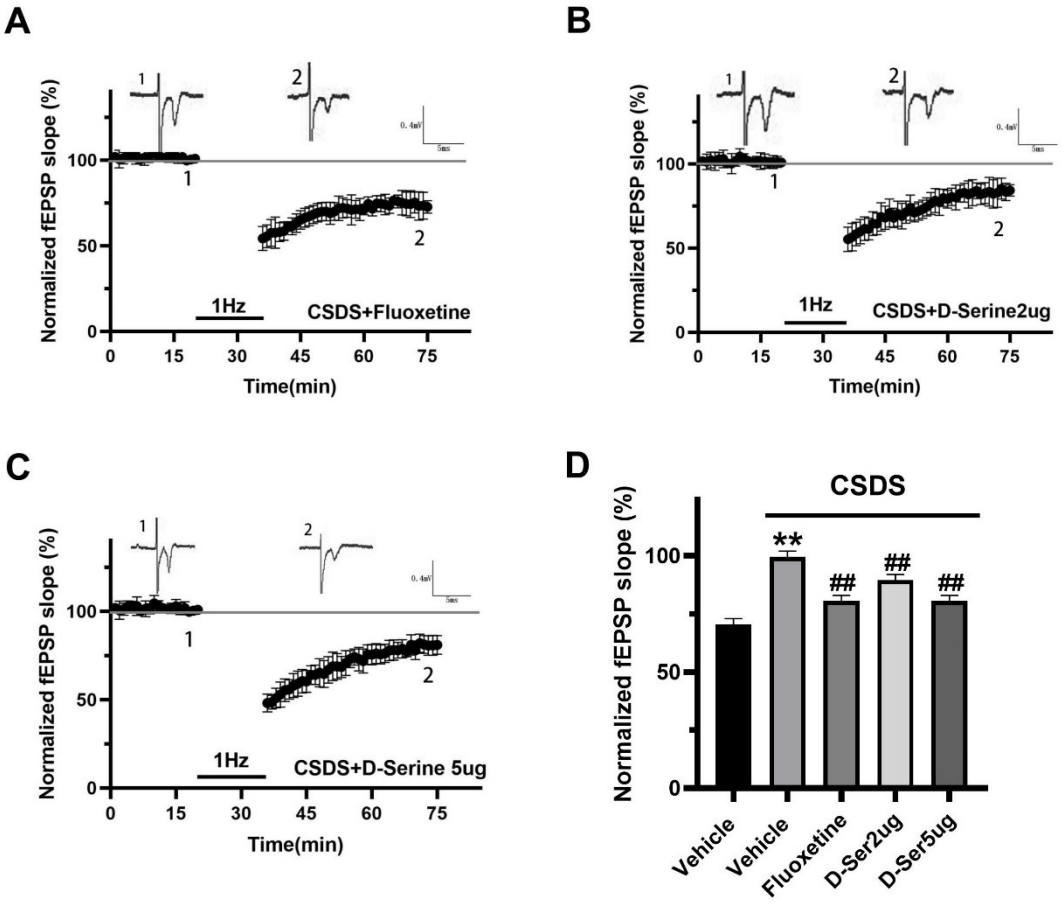

Figure 6.2 D-serine administration reversed the impaired NMDAR-dependent-LTD in NAc of CSDS mice. (A, B and C) Averaged data demonstrated that LTD was induced in CSDS+ fluoxetine mice, CSDS+ D-serine (2ug/perside) mice and CSDS+D-serine (5ug/perside) mice by LFS. (D) The column diagram demonstrated the level of LTD 40 min after LFS from control mice, CSDS mice, CSDS +fluoxetine mice, CSDS+ D-serine (2ug/perside) mice and CSDS+D-serine (5ug/perside) mice. Fluoxetine or D-serine administration reversed the damaged NMDA-LTD in NAc of CSDS mice. **p <0 .01 vs. control group; ##p < 0.01 vs. CSDS group. The superimposed fEPSP in the upper portion are recording from representative experiments taken at the time indicated by the number. Each point was the normalized mean ± SEM of eight slices.