Stressful events are inevitable in modern life. Although it is generally recognized that chronic stress causes cognitive deficits, the effects of acute stress on cognition are more complex. Acute stress can either impair or enhance memory consolidation depending on the emotional arousal of the task. For instance, Li et al. (2012) found that acute stress inhibits memory consolidation in the object recognition task, a relatively stress-free memory paradigm. Stress also affects the pre-attentive sensorimotor gating, a filtering mechanism that is thought to prevent sensory overload. Glucocorticoids, a class of hormones released during stress, can impair the pre-attentive prepulse inhibition of the acoustic startle response (PPI), a measure of sensorimotor gating (Richter et al., 2010).

The N-methyl-d-aspartate subtype of glutamate receptor (NMDAR) requires, in order to be activated, binding of both the agonist (glutamate) and a co-agonist (glycine or d-serine). Endogenously, d-serine is only formed by serine racemase (SR) and is the most potent co-agonist of the NMDAR. Importantly, the NMDAR regulates a variety of cognitive domains, including sensorimotor gating and memory. Additionally, the NMDAR has been extensively implicated in the effects of stress on cognition. However, the molecular mechanisms are not fully understood, and modulation of D-serine levels by acute stress has not been studied. Therefore, the question arises whether acute stress affects cognition through modulation of the D-serine pathway. Here we showed that acute stress decreases D-serine levels in the brain, possibly by a reduction of SR activity. We observed that acute stress reduced D-serine levels in the PFC and caused recognition memory and PPI deficits, all of which were prevented by administration of 1 g/kg D-serine. Taken together, these results contribute to understand stress physiology and its relevance to mental disorders.

References

Fig 1: Acute stress decreases D-serine levels and increases SR phosphorylation in the PFC. (A) D-serine levels in the PFC or (C) hippocampus homogenates after 90 min of restraint stress (Stress, N= 13) or in naive animals (Control, N= 12). SR was immunoprecipitated from (B) PFC or (D) hippocampus homogenates by immunodetection of phosphoserine and SR. Dots show the ratio between phosphoserine and total SR immunoreactivities. Different from control at *p<0.01 or ***p<0.0001.
Two-tailed t test. PFC, prefrontal cortex; HIP, hippocampus; P-ser, phosphoserine; SR, serine racemase.

Fig 2: D-serine prevents the effects of stress on cognition. Arrows indicate the time of D-serine (1 g/kg, i.p.) injection. Results represent the mean ± SEM. The numbers of mice for each group are shown inside the bars. (A) Acute stress impairs PPI induced by the 72 dB prepulse, which is prevented by a 1 g/kg injection of D-serine. (B) D-serine given during memory consolidation prevents the memory deficits caused by stress. The Saline+Stress group showed a significant lower recognition compared to the Saline+Control or the D-serine+Stress groups. *p<0.05
D-serine prevents cognitive deficits caused by acute stress
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Stressful events are inevitable in modern life. Although it is generally accepted that chronic stress promotes cognitive deficits, the effects of acute stress on cognition are more complex. Increasing evidence indicates that acute stress can disrupt cognitive functions mediated by the N-methyl-D-aspartate receptor (NMDAR), although the mechanisms are not fully understood yet. D-serine is the major endogenous co-agonist of the NMDAR, and is produced in the brain exclusively by the serine racemase. Importantly, serine racemase can be inhibited by phosphorylation on serine residues, resulting in lower D-serine levels. D-serine is crucial to long term potentiation induction and it also contributes to learning and memory. Also, D-serine is involved in sensorimotor gating, a filtering mechanism that is thought to prevent sensory overload. However, regulation of D-serine by acute stress remains to be investigated.

Here we examined whether the D-serine pathway is regulated by acute stress. We studied the biochemical and behavioral effects of acute restraint stress in C57BL/6 male mice. After 90 minutes of acute restraint stress, the animals had a large increase in plasma levels of corticosterone measured by radioimmunoassay (unpaired t test, p<0.0001, t=5.653). To study the impact of acute restraint stress on the D-serine pathway in the brain, we euthanized the mice after the acute restraint stress protocol and dissected the prefrontal cortex and the hippocampus. We used high performance liquid chromatography to study D-serine levels and we performed an immunoprecipitation followed by immunoblotting of the brain homogenates to study serine racemase phosphorylation. Interestingly, acute restraint stress decreased D-serine levels (unpaired t test, p<0.01, t=3.071) and increased serine racemase phosphorylation on serine residues (unpaired t test, p<0.0001, t=5.393) in the prefrontal cortex. In the hippocampus, neither D-serine levels nor serine racemase phosphorylation were altered by acute restraint stress. To study whether D-serine could prevent the effect of stress on memory, we performed an object recognition task. We tested the effect of acute restraint stress immediately after memory acquisition, during the memory consolidation phase. Recognition memory was impaired by acute restraint stress, which was prevented by peripheral administration of D-serine (1g/kg) 30 minutes before acquisition (Two-Way ANOVA, p<0.05) or immediately after acquisition, before the stress procedure (Two-Way ANOVA, p<0.05). However, D-serine had no effect on the memory impairment caused by stress when given one hour before memory retrieval. To investigate the impact of stress on sensorimotor gating, we measured the prepulse inhibition of the startle response (PPI). Acute restraint stress impaired PPI (Two-Way ANOVA, p<0.01), which was prevented by D-serine administration 20 minutes before stress (Two-Way ANOVA, p<0.01).

Taken together, our results show for the first time the interplay between acute stress and D-serine. We demonstrated that acute restrain stress lowered normal levels of D-serine, and that exogenous D-serine injections were efficient at restoring normal cognitive performance, in particular in memory and PPI. Future studies should address whether D-serine can be of clinical value on stress-related disorders.

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