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Research report

D-Cycloserine acts via increasing the GluN1 protein expressions in the frontal cortex and decreases the avoidance and risk assessment behaviors in a rat traumatic stress model

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HIGHLIGHTS

- Three day D-cycloserine (DCS) served as an adjuvant to extinction therapy in predator scent test in rats.
- GluN1 expressions were decreased in the amygdala and the dorsal hippocampus of rats with cat odor.
- Extinction training together with DCS upregulated GluN1 in the affected brain regions of rats.
- DCS with extinction training increased GluN1 protein levels in the frontal cortex.

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ABSTRACT

D-cycloserine (DCS), an FDA approved anti-tuberculosis drug has extensively been studied for its cognitive enhancer effects in psychiatric disorders. DCS may enhance the effects of fear extinction trainings in animals during exposure therapy and hence we investigated the effects of DCS on distinct behavioral parameters in a predator odor stress model and tested the optimal duration for repeated daily administrations of the agent.

Cat fur odor blocks were used to produce stress and avoidance and risk assessment behavioral parameters were used where DCS or saline were used as treatments in adjunct to extinction trainings.

We observed that DCS facilitated extinction training by providing further extinction of avoidance responses, risk assessment behaviors and increased the contact with the cue in a setting where DCS was administered before extinction trainings for 3 days without producing a significant tolerance. In amygdala and hippocampus, GluN1 protein expressions decreased 72 h after the fear conditioning in the traumatic stress group suggesting a possible down-regulation of NMDARs. We observed that extinction learning increased GluN1 proteins both in the amygdaloid complex and the dorsal hippocampus of the rats receiving extinction training or extinction training with DCS.

Our findings also indicate that DCS with extinction training increased GluN1 protein levels in the frontal cortex. We may suggest that action of DCS relies on enhancement of the consolidation of fear extinction in the frontal cortex.

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1. Introduction

Post-traumatic stress disorder (PTSD) is a unique mental disorder owing to the fact that the disorder naturally requires an etiological factor, a traumatic experience as a stressor to elicit the associated intrusive re-experiencing symptoms, avoidance behaviors, negative alterations in cognition and mood, alterations in

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arousal and reactivity levels which finally result in significant distress and functional impairment according to its recent definition in Diagnostic and Statistical Manual of Mental Disorders, 5th edition [1]. PTSD was moved from the category of anxiety disorders to a traumatic or stressor related disorders with the introduction of the DSM V. However the description of the disease extends to the second half of 19th century as hysteria defined by Pierre Briquet, traumatic neurosis by Hermann Oppenheim and choc nerveux by Jean Martin Charcot [38].

Despite the changes in the historical efforts of classification, the disorder has always been associated with a triggering etiologic factor. Therefore it is no surprise that PTSD was considered as the only mental disorder that involves an explicit conditioning session. Furthermore, it is closely associated with the "conditioning framework" [39]. From this view, a neutral stimulus may result in an unadaptive fear response when it was previously associated with an earlier traumatic experience. In other words, a memory trace may be formed between the neutral and the threatening events. Thus neutral cues may activate the threatening representations, triggering the anticipatory behaviors and anxiety [40].

A variety of pharmacological agents are available in the pharmacotherapy of the post-traumatic stress disorder. Current evidence is not sufficient to support the efficacy of any specific agent in the mainstream symptoms of PTSD, however the efficacy of cognitive behavioral therapy (CBT) has been well documented [2,26,36]. Therefore a tendency towards identifying pharmacological agents which can enhance the overall effectiveness of CBT and target the fear memory arose in the last decade. Hydrocortisone, propranolol, 3,4-methylenedioxy-*N*-methylamphetamine, riluzole and D-4-amino-3-isoxazolidone (D-cycloserine; DCS) are some of the promising agents [29]. DCS is an FDA approved anti-tuberculosis drug which has extensively been studied for its cognitive enhancer effects in psychiatric disorders. DCS may enhance the effects of fear extinction trainings in animals and exposure therapy in human studies [30]. Mechanism of action of DCS is through the *N*-methyl-D-aspartate subtype of glutamatergic receptors (NMDARS). The crucial role of the NMDARs in the fear extinction process has been reported by several researchers [13,19].

The aim of this current study is to show the efficacy of DCS on different aspects of the fear related behaviors in rats subjected to predator scent in extinction sessions as an animal model for exposure therapy and the expression of GluN1 (NMDAR NR1 subunit) in critical brain regions involved in PTSD.

2. Methods

2.1. Subjects

Thirty adult Wistar rats of both sexes supplied from Experimental Animal Research Center (DEHAMER, Marmara University, Istanbul) were used in the study. The number of male and female rats were equal in all groups. Upon getting approval from the University Local Ethical Committee, the rats were maintained in 12 h reverse light-dark circle (lights on 7 p.m.), at a constant room temperature of $22 \pm 2\,^{\circ}C$ and a humidity ratio of $50 \pm 5\%$. The reason that reverse light-dark cycle to be used is that the rats are nocturnal animals so that the procedures would be performed during the active period of the rats. Rats were fed ad libitum with standardized rat food and water. Each rat was handled once a day for 10 min by the same researcher. During this period, 6 rats were housed per cage but following stress procedures the rats were housed singly. Each experimental group consisted of 6 rats. The rats were assigned into 5 groups where the first group consisted of non-traumatized controls and the second traumatized controls. These 2 groups received no treatment. The other three groups were also traumatized and received either physiological saline or DCS for 3 or 5 days together with extinction procedures.

2.2. Experimental apparatus

The apparatus in which the rats were exposed to odor or no-odor blocks was a plexiglass box with $100 \times 15 \times 50$ cm dimensions allowing the rat a back and forth movement. The apparatus was reproduced according to [3]. The box had clear walls enabling video recording and the front wall of the box was divided into 3 equal segments with a red marker. Wooden blocks covered with cotton fabric were used to serve as predator odor stress stimulus. Blocks were left in the bed of street cats for 2 days prior to testing and rubbed against the fur around the cats neck prior to the experiment. Identical clean blocks were used as no odor control blocks.

2.3. Procedure

Stimulus block was placed at one end of the box. A rat was placed at the other end and allowed to move freely in the box for 10 min. Sessions were recorded by a video device under red light (7 W). Behavioral parameters were assessed according to the cat fur odor model [3]. The analyzed behavioral parameters included were:

Far location: time spent in the far segment of the experimental apparatus from the compartment where block is placed.

Contact duration: time spent in contact with the block.

Far location and contact duration; former being directly and the later inversely asseses the avoidance.

Freezing time: total immobility time.

Location change: total number of location change in between 3 compartments. This parameter is scored when all 4 limbs of the animals move to another segment. Activity is measured by this parameter.

Stretch attend duration: duration of the subject's stationary position where the body is elongated with a low back when the subject is facing the stimulus block with placing fore and hind limbs far apart.

Stretch approach duration: duration of the subject's movement toward stimulus block with a low back and elongated posture.

Stretch attend and stretch approach were considered as the risk assessment behaviors.

The phases of the procedure were as described:

Habituation: from day 1 to day 4, each rat was placed in the test apparatus for 10 min for 4 consecutive days in the absence of the stimulus block.

Cat odor block exposure: on day 5, the rats were exposed to cat odor block while control group rats were exposed to no-odor blocks. Each session for a subject was videotaped for 10 min and the behaviors were assessed.

Extinction: days 6 through 8, 3 groups of rats; days 6 through 10, another extra group of rats were exposed to no-odor block in the apparatus for 10 min daily. Two groups of rats experiencing the extinction procedure also received subcutaneous 15 mg/kg DCS (Sigma, USA) 15 min before each session while the other extinction group as well as the non-extinction groups were treated with subcutaneous physiological saline (0.1 ml/100 g rat).

Test: On day 9, 4 groups were tested in the same apparatus with a no-odor block. On day 11, only the rats that received DCS injections for 5 days were exposed to no-odor blocks.

The procedures and treatments of all groups were summarized in Table 1.

2.4. Tissue preparation and immunoblotting

All chemicals were purchased from Sigma (St Louis, MO, USA) unless indicated. The rats were decapitated following high

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