Original Article

The Role of Cyclooxygenase 2 in the Cognitive Impairment Induced by Alcohol or Stress in Rats

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Abstract

Background: Cognitive impairment is an unpleasant and progressive mental disorder characterized by learning and memory disabilities. Stress and alcohol are two known environmental factors that increase cognitive impairment. This study was designed to evaluate the relative role of cyclooxygenase 2 in alcohol or stress-induced cognitive impairment. **Materials and Methods:** Male Wistar rats were randomly divided into groups with six rats in each. The groups included sham, control, alcohol (15% ethanol in drinking water), and restraint stress (restraint 6 h per day). Three separated groups received celecoxib at a dose of 20 mg/kg in addition to those listed above. The treatments continued daily for 28 days. The object recognition task (ORT) and Morris water maze (MWM) are used to evaluate the learning and memory. **Results:** Alcohol or restrain stress significantly increased the time and distance needed to find the hidden platform in MWM. Furthermore, they decreased the recognition index in ORT compared to the control group. Administration of celecoxib significantly decreased the required time and traveled distance to reach the platform in alcohol-treated animals but not in the stress-exposed rats. Celecoxib also significantly increased the recognition index both in alcohol- or restraint stress-exposed animals. **Conclusion:** We found that either alcohol or restraint stress impairs memory in rats. In MWM, celecoxib improved the alcohol-induced memory impairment but could not show a reduction in memory deterioration due to restraint stress. In ORT, celecoxib reversed memory impairment due to both alcohol and restraint stress.

Keywords: *Celecoxib, Cognition disorders, Ethanol, physical examination, Restraint, Physical*

Introduction

Cognitive impairment refers to a disorder in which the recalling of past information and memories as well as the learning abilities is perturbed. Most mental disorders including major depression, psychosis as well as the neurodegenerative disorders usually lead to cognitive impairment.[1] Cognitive impairment is a well-known clinical output of Alzheimer's disease which is characterized by hyperphosphorylation of tau proteins and extensive accumulation of amyloid-beta plaques.[2] The incidence of cognitive impairment depends on genetic and epigenetic factors. A wide range of environmental agents that are present in air pollution or daily food as well as physical and psychological stressors plays an important role in the formation and development of cognitive impairment.[3-5] The two main factors affecting learning and memory are alcohol consumption and stress exposure. In fact, alcohol or stress will negatively impair the cognitive function of animals and humans. However, their final effect depends on the severity and duration of the exposure.[6]

Chronic stress induces structural changes in the brain including a decrease in hippocampus layer volume. It also triggers the neurodegenerative events leading to disruption of brain function.[7] It has been reported that stress decreases the learning competence and impairs different types of memories.[8] A wide range of mechanisms is proposed for the cognitive deteriorations induced by stress. In particular, oxidative stress, neural apoptosis, neuroinflammation, impaired synaptic plasticity, and altered neurotransmission of glutamate and aspartate are some well-known mechanisms by which stress causes cognitive impairment.[9,10]

Alcohol intake is another important environmental factor inducing cognitive impairment. Like stress, alcohol impairs the

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brain structure and its connections, decreases the number of neurons, and shrinks the hippocampus size. In addition, the mental and physiological processes including learning and memory are hampered both in animals and humans, especially with chronic alcohol.[11,12] Moreover, the effects of alcohol also depend on the amount of its consumption, which is documented by higher incidence and intensity of learning disabilities and dementia in heavy drinkers.[13] Alteration of neural metabolism, oligodendrocytes and glia cells' injury, reduction of neurotrophic factors, oxidative stress, neural apoptosis, and a decline in central cholinergic activity are the most important mechanisms involved in the ethanol-induced cognitive impairment.[11,12,14] As it is clear, many of the mechanisms that are implicated by stress or ethanol to induce cognitive impairment are the same.

Cyclooxygenase II (COX-II), which is a rate-limiting step in the formation of prostaglandins (PGs) from arachidonic acid, is also involved in the pathophysiology of different types of cognition impairment. In fact, some memory impairing agents induce the expression of central COX-II, leading to a wide range of pathological cascades in the brain. Of particular note, formation of reactive oxygen species, neuroinflammation, neuronal apoptosis, and a decrease in neurotrophic factors are among the processes depending on COX-2.[15] On the other hand, cyclooxygenase inhibitors such as indomethacin and naproxen improved cognitive impairments, suggesting COX inhibition as an effective therapeutic strategy in some central nervous system disorders caused by neuroinflammation.[16,17] Celecoxib is a selective COX-II inhibitor which can keep the beneficial effects of COX-I activity while inhibiting the destructive effects of COX-II.[18]

Even though it is reported that many mechanisms are involved in cognitive impairment caused by stress or alcohol, the role of COX-II has not been studied clearly. The current study aims to investigate the relative role of COX-II activity in restraint stress or alcohol-induced cognitive impairment in rats as a stimulant or sedative toxic condition, respectively.

Materials and Methods

Reagents and chemicals

Celecoxib was purchased from Amin Pharmaceutical Company (I.R.Iran, Batch number: CEL (956) 07-19). Ethanol 96% EMPROVE® was purchased from the Merck Company (Germany, CAS number 64-17-5).

Animals

Male Wistar rats weighted 200 ± 20 g were subjected to this experimental study. Animals were supplied from the animal house, Isfahan University of Medical Sciences, Isfahan, I. R. Iran. They were housed six per cage and maintained on a 12-h light-dark cycle in an air-conditioned constant room temperature (22°C ± 3°C), with food and water made available *ad libitum*. The Ethics Committee for Animal Experiments at Isfahan University of Medical Sciences approved the study (Approval code: IR.MUI.RESEARCH.REC.1398.539), and all experiments were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

Experimental procedure

Exposure to restraint stress

Restraint stress was performed by the use of a porous restrainer tube (15 × 5). It could be adjusted in length according to the rat's size. In the restrainer, animals just could slightly go back and stretch their legs. For the restraint stress procedure, the animal was held in the tube for 6 h per day in a well-ventilated room.[19]

Treatment schedule

Animals were randomly divided into seven groups with six rats in each. The experiment was performed as following:

Sham group

This group received normal drinking water and without any stressful conditions.

Control group

This group received normal drinking water, without any stressful conditions, and received drug vehicle (carboxymethyl cellulose [CMC] 0.1% in 1 mL water) every day by gavage to end of experiment.

Celecoxib group

This group received normal drinking water, without any stressful conditions, and received 20 mg/kg celecoxib every day by gavage to the end of the experiment.

Alcohol group

This group received ethanol 15% in their drinking water (initiated with 5% ethanol and increased 5% every 2 days until ethanol concentration of 15% achieved) and was gavaged drug vehicle to the end of the experiment.

Alcohol + celecoxib group

This group received ethanol 15% in their drinking water and 20 mg/kg celecoxib daily by gavage to the end of the experiment.

Restraint stress group

This group received normal drinking water and exposed to restraint stress (6 h/day) for 28 days.

Restraint stress + celecoxib group

This group received normal drinking water and exposed to restraint stress (6 h/day) and was gavaged with 20 mg/kg celecoxib every day for 28 days.

Alcohol and water bottles were removed from non- restrained groups during the restraint stress procedure and celecoxib suspension was prepared freshly each time by dispersing in CMC.

Cognitive behavior assessment

On day 28, memory of all rats was evaluated using object recognition task (ORT) and the Morris water maze (MWM).

Object recognition task

The ORT test is a method which examines unconditional memory based on the animal's desire to explore a new object and to recall an old object that has already been explored. Novel ORT consisted of three sessions: (1) habituation, (2) familiarization, and (3) test session. A black-colored open field box (36 cm × 50 cm × 36 cm) was used in this test. In the habituation phase, the rat was habituated in the open field area and allowed to explore for 5 min twice a day. On the 2nd day, familiarization phase was carried out by placing two small identical objects (rectangular plastic blocks) in the open-field apparatus. Afterward, the rat was placed in the open field by keeping the position of the head opposite to the objects and allowed to explore for 5 min. After 1 h, a test session was carried out by placing a novel object (a small cylindrical wooden block) in place of one plastic box. Thereafter, each rat was explored for 3 min in the open field. The objects and open field area were repeatedly cleaned with alcohol (70% v/v) to avoid the olfactory cues. Recognition index (a ratio of the time spent with a novel object and the total time spent with both of the objects) during the test session was calculated according to the following formula. Total exploratory time was also recorded during the experiment.[20]

$R = N/(N + F) \times 100$

N: Total time spent exploring a new object

F: Total time spent exploring a familiar object

R: Criteria for recognizing, a relative measure to examine the difference between exploring a new object and a familiar object.

Morris water maze procedure

The MWM is a test of spatial learning for rodents that relies on distal cues to navigate from start locations around the perimeter of an open swimming arena to locate a submerged escape platform. MWM consists of a circular tank (150 cm diameter and 80 cm height), containing opaque water (25°C ± 1°C). The platform (10 cm diameter) was kept 2 cm below the water level. The animal was kept in the tank facing toward the tank wall and allowed to find the platform for 120 s during the learning phase. If the animal failed to locate the platform in 2 min, then the animal was placed on the platform for 30 s. Four trials (per trial per quadrant) per day were given to each animal for 4 consecutive days and 5-min time interval was maintained between each subsequent trial. On the 5th day, escape latency (i.e., time taken by the animal to find the hidden platform) and the traveled distance (i.e., path spent by the animal to find the platform) were calculated.[21]

Statistical analysis

The data were expressed as means ± standard error of the mean, these were analyzed by GraphPad Prism v. 6 software. The differences between the control and treatment groups were evaluated by one-way ANOVA followed by the Tukey *post hoc* test. $P < 0.05$ between groups was assumed as a statistically significant level.

Results

The effect of restraint stress or alcohol intake on escape latency time and traveled distance in Morris water maze

Daily restraint stress for 6 h/day within 28 consecutive days significantly increased the time required and path spend to find the hidden platform (latency time and traveled distance, respectively) in the MWM test compared to the control group ($P < 0.01$) [Figure 1a and b]. Furthermore, animals treated with 15% alcohol in drinking water for 28 days showed a significant increase in the latency time and traveled distance in comparison to the control animals ($P < 0.01$) [Figure 1a and b].

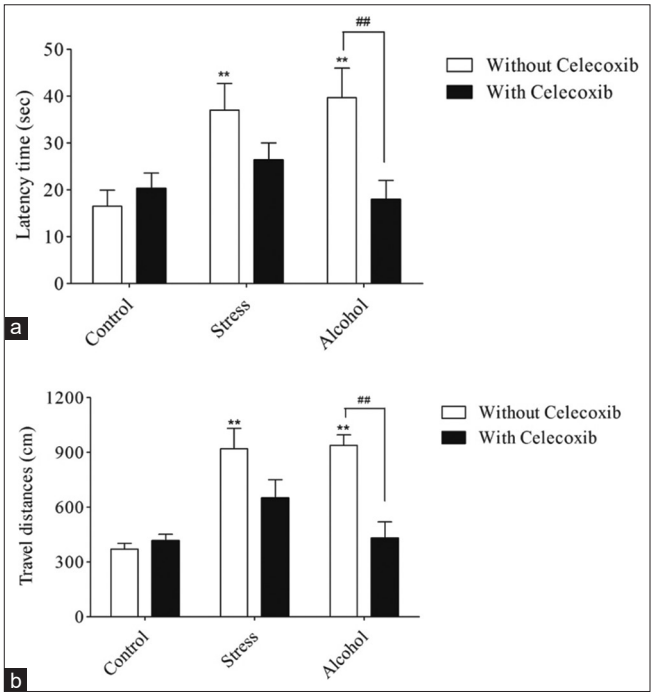

Figure 1: The effect of celecoxib administration on the latency time (a) and traveled distance (b) in Morris water maze for rats exposed to stress or alcohol. The data are presented as mean ± standard error of the mean of 6 rats per group. **$P < 0.01$ shows a statistically significant difference compared to the control group. ##$P < 0.01$ shows a statistically significant difference with alcohol-treated animals

The effect of celecoxib on latency time and traveled distance of rats exposed to restraint stress in Morris water maze

Administration of celecoxib at 20 mg/kg in rats exposed to 6 h daily restrictive stress for 28 consecutive days did not cause a significant change in the escape latency or traveled distance to find the platform compared to the stress-exposed animals [Figure 1a and b].

The effect of celecoxib on latency time and traveled distance of rats treated with alcohol in Morris water maze

Celecoxib at the dose of 20 mg/kg when given orally for 28 days to the 15% alcohol-treated rats remarkably decreased both escape latency and traveled distance in the MWM ($P < 0.01$) [Figure 1a and b].

The effect of restraint stress, alcohol intake, and addition of celecoxib on the swimming speed of rats in Morris water maze

The swimming speed to find the hidden platform in MWM of all studied rats including restraint stress- and alcohol-exposed animals with or without celecoxib was not statistically different [Figure 2].

The effect of restraint stress or alcohol intake on the recognition index (R) in object recognition task

Exposure to restraint stress 6 h/day for 28 days caused a significant decrease in the R index in ORT ($P < 0.001$). Administration of 15% alcohol for 28 days also caused a significant decrease in R index in the ORT compared to the control ($P < 0.001$) [Figure 3].

The effect of celecoxib on the recognition index (R) of restraint stress- or alcohol-exposed animals in object recognition task

Celecoxib at 20 mg/kg significantly increased the R index in rats exposed to 6 h daily restrictive stress in ORT ($P < 0.001$). Celecoxib also efficiently altered the R index in rats that received 15% alcohol in drinking water for 28 days ($P < 0.001$) [Figure 3].

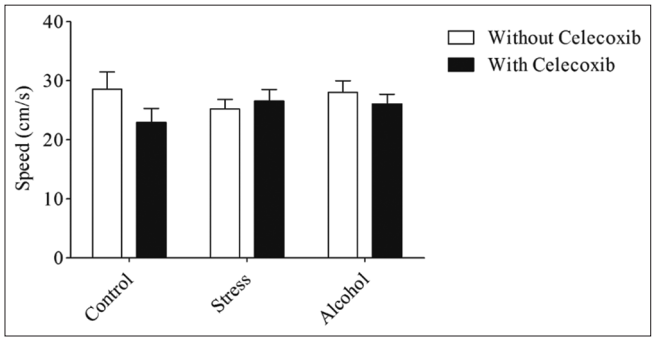

Figure 2: The swimming speed for all studied groups tested in Morris water maze. The data are presented as mean ± standard error of the mean of 6 rats per group. There are no significant changes in swimming speed of rats in all groups

Discussion

Stress exposure and alcohol intake are known as two main environmental factors causing cognitive impairment in structural and physiological aspects of the brain in animals and humans. Many researchers use a type of stress when they are going to study its effect on the experimental animal's activity named restraint stress, in which the animals are restricted from movement for a long time every day.[21,22] Alcohol is often administered to the animals in drinking water in a high concentration to simulate the people who are heavy drinkers. We used the restraint stress and 15% alcohol for 1 month to make a real condition similar to that happens in humans for a long time. The MWM is one of the most reliable tasks for the evaluation of spatial memory, in which there is no need for rewards such as food, so it does not interfere with the animals' response. Moreover, factors that influence the animals' behavior such as visual acuity, motor function, and motivation can be measured and excluded from the answers in this maze.[23] In addition, another method called ORT is used to evaluate non-spatial memory. This maze relies on rodent natural proclivity for exploring novelty. This is relatively fast, no stressful, and enough efficient method with no need for numerous training sessions or any positive or negative reinforcements to motivate behavior.[20]

We found that exposure to restraint stress significantly impaired the spatial memory of rats in MWM compared to the control animals. It also remarkably decreased the animal's memory of the old object in the ORT paradigm. Meanwhile, restraint stress did not change the motor activity of rats in both the tasks. This is in accordance with studies showing that restraint stress, even short-term (5 days), decreases the memory performance in a mirror chamber test.[24] Likewise, exposure to restraint stress for 21 days is associated with impaired spatial memory.[25] Furthermore, restraint stress could result in impairments in both memory and behavior of rats, possibly through increased oxidative stress in the brain.[26]

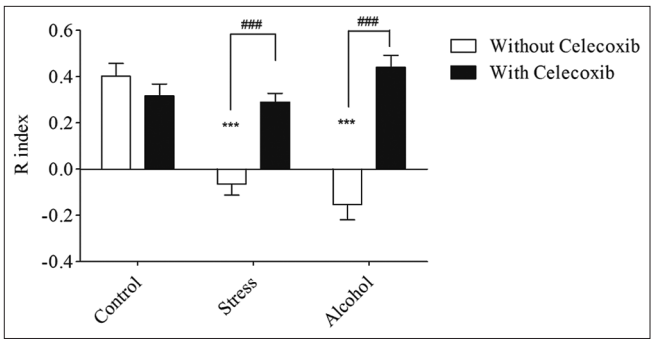

Figure 3: The effect of celecoxib on the recognition index (R) in object recognition task for rats exposed to stress or alcohol. The data are presented as mean ± standard error of the mean of 6 rats per group. ***$P < 0.01$ shows a statistical difference compared to the control group. ###$P < 0.01$ shows a statistically significant difference with respective without celecoxib animals

We also found that 15% ethanol for 28 days significantly reduced the spatial and non-spatial memory compared to the control animals. Motor activity did not differ between the alcohol-treated and normal animals both in MWM and ORT (data not shown). Accordingly, ethanol hampers memory formation and retrieval in MWM and passive avoidance learning tests.[27,28] In this regard, ethanol-induced memory impairment in MWM was associated with enhanced acetylcholinesterase activity, increased oxidative-nitrosative stress, and increased levels of inflammatory cytokines (tumor necrosis factor-α, interleukin-1 β, and Transforming growth factor-β) in both cerebral cortex and hippocampus.[29]

In the second step of our study, we administered celecoxib, a selective COX-II inhibitor, together with restraint stress or alcohol to investigate the role of COX-II in the pathobiology of cognitive impairment induced by restraint stress or alcohol.[18] We found that celecoxib when administered to the normal animals altered animals' performance neither in MWM nor in ORT. This implies that COX-II, *per se*, may not be a pivotal player in the memory of normal trained animals in MWM or ORT. Meanwhile, celecoxib, when orally administered to the alcohol-treated animals, clearly reversed ethanol-induced memory impairment and even improved it to a normal level both in MWM and ORT. This indicates a potential role for COX-II induction in alcohol-induced spatial and non-spatial memory impairment. These results are consistent with COX induction in the brain by several memory-impairing agents.[18,30]

Given that celecoxib as well as its congeners inhibit the synthesis of prostaglandins, a role for these molecules is plausible in celecoxib-induced neuroprotection. In this regard, activation of PG receptors, belonging to the superfamily of G protein coupled receptors (GPCRs), may induce the activation of different G proteins or arrestins, which then relay the signal to intracellular effector molecules.[31] Of particular note is the mitogen activated protein kinases (MAPKs), which play a pivotal role in different cellular processes including cellular proliferation, neural activity and cognitive function.[32,33] Recently, alteration of cellular signaling with different biased ligands acting on the same GPCR has gained significant attention, and these ligands may provide better efficacy devoid of on-target side-effects.[34] In addition, an interplay between COX-2 and nicotinic[35] or serotoninergic[36] signaling may play a role in cognitive protection due to celecoxib, which demands further elucidation.

Celecoxib when administered to the stress-exposed animals reverted the impaired memory to the normal level just in ORT task but failed to improve the stress-induced memory dysfunction in MWM paradigm. This implies that even though COX-II plays an important role in the mechanism of action for restraint stress in non-spatial memory, it may not be as necessary for the restraint stress to impair the spatial memory. Taking together, COX-II plays a more important role in memory impairment caused by alcohol rather than restraint stress.

Conclusion

Long-term exposure to the restraint stress or ethanol leads to memory loss in rats when evaluated in MWM or ORT. The activation of COX-II is an essential step in the pathological events of both spatial and non-spatial memory dysfunction following the intake of alcohol. Meanwhile, COX-II role in stress-induced cognitive dysfunction may be limited to non-spatial memory, and other mechanisms seem to be involved in the impairment of spatial memory after exposure to the restraint stress.

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Conflicts of interest

There are no conflicts of interest.

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