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Original Article

Caffeic Acid Exerts Anticonvulsant Effects on Mice by Modulating Nitrite Imbalance in the Prefrontal Cortex: An Interventional Study Using Nitric Oxide Mediators

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Abstract

Introduction: Nitric oxide (NO) is implicated in the etiology. Caffeic acid (CA) possesses neuroprotective properties in various animal models. This study assessed the anticonvulsant properties of CA by investigating its effects on nitrergic transmission in the prefrontal cortex (PFC) during pentylenetetrazol (PTZ)-induced seizures in mice, using NO precursors and synthesis inhibitors.

Methods: Sixty-four male mice were randomly divided into eight groups, including those administered intraperitoneal normal saline, CA at different doses (1, 4, and 8 mg/kg), diazepam, Nomega-nitro-L-arginine methyl ester hydrochloride (L-NAME), a NO synthase inhibitor (10 mg/kg), L-arginine (L-arg), a NO precursor (100 mg/kg), effective dose of CA (8 mg/kg) with L-arg, and sub-effective dose of CA (1 mg/kg) + L-NAME, correspondingly. Latency to seizure and nitrite levels in the PFC were measured, and data were analyzed with the one-way analysis of variance followed by Tukey's post-hoc test.

Results: Two doses of CA [4 ($P<0.0001$) and 8 mg/kg ($P<0.0001$)] and L-NAME ($P<0.0001$) augmented the latency to seizure while reducing nitrite levels in the PFC [doses 1 ($P<0.0001$), 4 ($P<0.0001$), and 8 mg/kg ($P<0.0001$)], and L-NAME ($P<0.0001$). The co-injection of L-NAME potentiated ($P<0.0001$) the effect of the sub-effective dose of CA (1 mg/kg) on latency to seizure, whereas L-NAME and L-arg potentiated ($P<0.0001$) and mitigated ($P=0.0018$) the effects of corresponding CA doses on PFC's nitrite level, respectively.

Conclusion: Our findings demonstrated a probable role for NO in the anticonvulsant properties of CA in PTZ-induced seizures. Diminished nitrergic neurotransmission partly mediated the anticonvulsant effect of CA on male mice.

Keywords: Caffeic acid, Anticonvulsant, Nitric oxide, Prefrontal cortex

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Introduction

A seizure is a heterogeneous neurological disorder that is characterized by abrupt, intermittent, and extreme electrical discharges in the central nervous system, leading to abnormal behavior and symptoms, including loss of consciousness (1). In addition, it is linked with a higher load of comorbidity and lower quality of life (2). Around 1% of people suffer from seizures (3), and regardless of the development of new anticonvulsants, nearly 40% of them do not adequately respond to anticonvulsants (4). Moreover, commonly prescribed anticonvulsants have several side effects (5). There is, therefore, a pressing need to identify and introduce new agents with anticonvulsant potential and fewer side effects.

Nitric oxide (NO) is a neurotransmitter in the central nervous system. Additionally, NO is produced from the precursor of L-arginine by NO synthase (NOS) enzyme isoforms. NOS has three isoforms, including neuronal NOS, endothelial NOS, and inducible NOS (6, 7). It is well known that NO, in a bimodal manner, modulates seizure susceptibility, with excessive increases or decreases in NO increasing or decreasing vulnerability to seizures (8, 9). According to prior research, NO is significantly involved in the pathophysiology of seizures (10). The induction of seizures is accompanied by an increase in nitrite levels in brain areas, such as the prefrontal cortex (PFC) (11, 12). In this regard, a couple of researchers have proposed that some effective anticonvulsants decrease nitrite levels in the brain (13, 14). Hence, the extenuation of nitrite levels in the brain can be considered a potential target for the management of seizures.

Conventionally, medicinal plants and their active components have attracted the attention of scientists for the management of several diseases, such as seizures (15). Caffeic acid (CA: 3, 4-hydroxycinnamic acid) is a polyphenolic ingredient that is abundantly found in plants and fruits (16). Earlier studies have reported several pharmacological properties for CA, including analgesic, anti-Alzheimer's disease, and anti-inflammatory activities (17-19). The neuroprotective effects of CA have been reported previously. In this concept, different researchers have confirmed the anxiolytic, antidepressant, and memory-improvement effects of CA

(16, 20, 21). Combating CA-induced neurotoxicity has been demonstrated in some studies (22, 23). Other studies have described the anticonvulsant effects of CA (24, 25), though the mechanisms by which CA mediates these effects remain incompletely elucidated.

To the best of our knowledge, no study has so far investigated the exact mediating mechanism that is involved in the anticonvulsant effect of CA.. Considering the role of NO in the pathophysiology of seizures, this study aims to evaluate the anticonvulsant properties of CA in pentylenetetrazol (PTZ)-induced seizures in male mice, addressing its potential effects on nitrite transmission in the PFC.

Materials and Methods

Animals

Sixty-four male NMRI (Naval Medical Research Institute) mice (aged between 9 weeks and 12 weeks and weighing 20–30 g) were utilized in this study. The animals were obtained from the Royan Institute in Isfahan, Iran. They were housed under standard laboratory conditions, including a controlled temperature of 23 ± 1°C, a 12-hour light/dark cycle (lights on at 8:00 a.m.), and had unrestricted access to food and water.

Study Plan

Mice were randomly allocated to 8 groups and injected with normal saline (10 mL/kg), CA at doses of 1 mg/kg, 4 mg/kg, and 8 mg/kg, diazepam (10 mg/kg), L-NAME, a NOS inhibitor (10 mg/kg), L-arginine (L-arg), a NO precursor (100 mg/kg), and the effective dose of CA (8 mg/kg) with L-arg, as well as the sub-effective dose of CA (1 mg/kg) plus L-NAME, correspondingly. Additionally, all substances were dissolved in normal saline and administered intraperitoneally (IP) at a dosage volume of 0.1 mL per 10 g of body weight. Moreover, PTZ was delivered via intravenous injection. Furthermore, CA was administered 60 minutes, and L-arg and L-NAME were administered 45 minutes before seizure induced by PTZ. To identify the possible underlying mechanisms mediated by the anticonvulsant effect of CA, L-NAME was co-administered with a sub-effective dose of CA (1 mg/kg), and L-arginine was co-injected with an effective dose of CA (8 mg/kg). Further, the sub-effective and effective doses of CA were selected based on the outcomes of separate CA administrations. Likewise, the dose and timing of drug injections were chosen based on previous research and our pilot study (26, 27). After the measurement of latency to seizure, mice were euthanized under deep anesthesia using ketamine (60 mg/kg, IP) and xylazine (10 mg/kg, IP). The brains were dissected out, and the PFC was separated. To reduce potential bias, all tests were conducted in a blinded manner. In addition, the sample size per group was set at 6–8 and 3–4 mice for behavioral evaluations and molecular studies, respectively, which is consistent with that of previous studies, demonstrating that this range yields reproducible, statistically robust outcomes (28, 29).

Induction and Valuation of Latency to Seizure

To induce seizures, PTZ was administered intravenously. Further, mice were briefly restrained to allow accurate placement of a 30-gauge winged infusion set into the tail vein. While the animals remained freely mobile, PTZ (0.5%) was infused at 1 mL/min using a seizure pump. The infusion was immediately stopped upon the appearance of forelimb clonus or generalized clonic activity, typically beginning with running followed by loss of the righting reflex. Finally, the time elapsed until seizure onset was recorded as seizure latency (30).

Dimension of the Nitrite Level in the Prefrontal Cortex

Nitrite concentrations in PFC homogenates were measured using the Griess reaction. In brief, 100 µL of each sample was mixed with 100 µL of Griess reagent and incubated at room temperature for 10 minutes. Then, the absorbance was read at 540 nm using an automated microplate reader. Ultimately, nitrite levels were quantified by comparison to a sodium nitrite standard curve (Sigma, USA) and expressed as micromoles of nitrite per milligram of protein (31).

Statistical Analysis

GraphPad Prism (version 8) was applied for statistical analysis. To assess data normality for selecting the analysis type, the Kolmogorov–Smirnov test was performed, indicating that the data are parametric. Additionally, the Forsythe test was employed to evaluate data homogeneity. Data were presented as means ± standard deviations (SD) and analyzed with one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. $P < 0.05$ was considered statistically significant.

Results

Effect of Caffeic Acid on Latency to Seizure

The results of the one-way ANOVA followed by Tukey's post-hoc analysis (Figure 1) confirmed that mice treated with CA at doses of 4 mg/kg (mean ± SD = 15.05 ± 1.510, $P < 0.0001$) and 8 mg/kg (mean ± SD = 15.72 ± 1.258, $P < 0.0001$), as well as those receiving L-NAME (mean ± SD = 14.80 ± 2.606, $P < 0.0001$), exhibited a significantly longer latency to seizure compared to the saline-treated group (mean ± SD = 4.330 ± 0.8122). Additionally, co-treatment with L-NAME and a sub-effective dose of CA (1 mg/kg, mean ± SD = 16.01 ± 1.150) substantially prolonged seizure latency relative to the administration of the sub-effective dose of CA alone (mean ± SD = 7.566 ± 1.462) ($P < 0.0001$). Likewise, combining L-arginine with an effective dose of CA (8 mg/kg, mean ± SD = 16.38 ± 2.833) resulted in a notable increase in seizure latency compared to the group treated with L-arg alone (mean ± SD = 6.512 ± 2.845) ($P < 0.0001$).

Effect of Caffeic Acid on the Nitrite Level in the Prefrontal Cortex

Analysis using one-way ANOVA followed by Tukey's post hoc test (Figure 2) revealed that nitrite levels in the

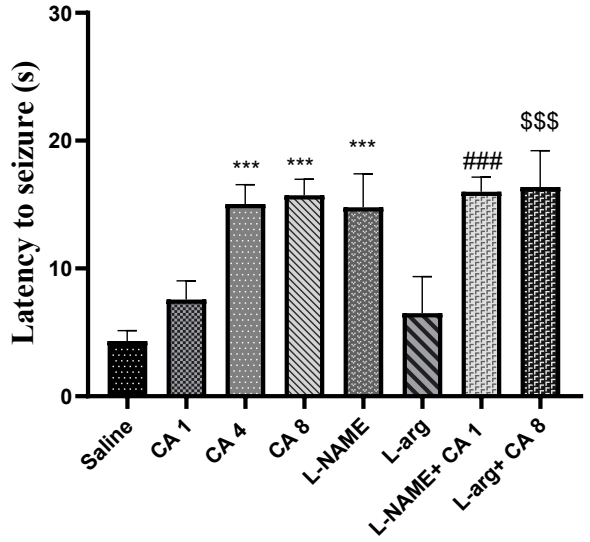

Figure 1. Effect of CA Alone and in Combination With a Precursor or Inhibitor of NO on the Latency to Seizure Across Experimental Groups
Note. Data were expressed as means ± standard deviations and analyzed using one-way ANOVA followed by Tukey's post-hoc test. *** indicates a statistically significant difference compared to the saline-treated group ($P < 0.0001$), and $$$ denotes a significant difference relative to the L-arginine-treated group ($P < 0.0001$). Moreover, ### represents a significant difference compared to the group treated with CA at 1 mg/kg ($P < 0.0001$). ANOVA: Analysis of variance; NO: Nitric oxide; CA: Caffeic acid; L-arg: L-arginine; L-NAME: Nomega-nitro-L-arginine methyl ester hydrochloride

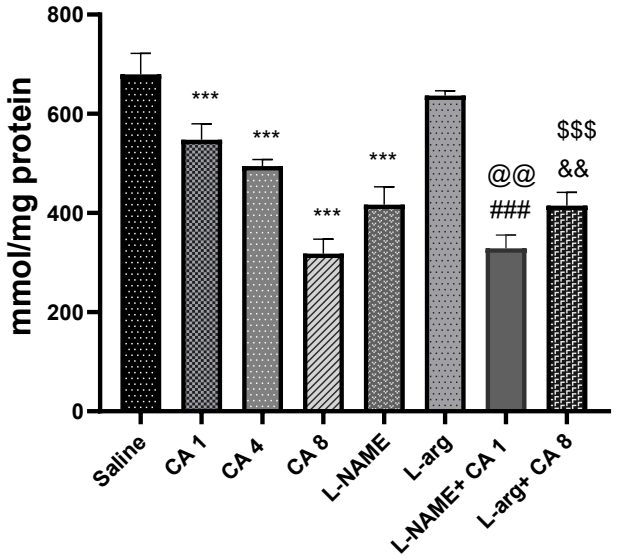

Figure 2. The Effect of CA Alone and in Combination With a Precursor or Inhibitor of NO on the Nitrite Concentrations in the PFC
Note. Data were expressed as means ± standard deviations and analyzed using one-way ANOVA followed by Tukey's post-hoc test. Statistical significance was denoted by the following symbols: *** $P < 0.0001$ vs. saline-treated mice, ### $P < 0.0001$ vs. CA (1 mg/kg)-treated mice, $$$ $P < 0.001$ vs. L-arginine-treated mice, @@ $P = 0.0049$ vs. L-NAME-treated mice, and && $P = 0.0018$ vs. CA (8 mg/kg)-treated mice. CA: Caffeic acid; L-arg: L-arginine; L-NAME: Nomega-nitro-L-arginine methyl ester hydrochloride

PFC were sharply reduced in mice treated with CA at doses of 1 mg/kg (mean ± SD = 547.5 ± 32.13, $P < 0.0001$), 4 mg/kg (mean ± SD = 494.8 ± 12.97, $P < 0.0001$), and 8 mg/kg (mean ± SD = 318.0 ± 29.29, $P < 0.0001$), as well as in those receiving L-NAME (mean ± SD = 417.0 ± 36.04, $P < 0.0001$), compared to the saline-treated control (mean ± SD = 679.5 ± 42.26). Additionally, the co-administration of L-NAME with a sub-effective dose of CA (1 mg/kg, mean ± SD = 328.8 ± 26.84) resulted in a considerable decrease in PFC nitrite levels compared to both the CA-only group (mean ± SD = 547.5 ± 32.13, $P < 0.0001$) and the L-NAME-only group (mean ± SD = 417.0 ± 36.04, $P = 0.0049$). Conversely, combining L-arginine with an effective dose of CA (8 mg/kg, mean ± SD = 414.8 ± 26.94) noticeably elevated nitrite levels relative to CA alone (mean ± SD = 318.0 ± 29.29, $P = 0.0018$) while still showing a significant reduction compared to the L-arginine-only group (mean ± SD = 636.5 ± 10.21, $P < 0.0001$).

Discussion

CA can increase the latency to PTZ-induced seizures in mice, which is in line with the results of the present study. Consequently, CA lessened nitrite levels in the PFC. Interventional study with the inhibitor and precursors of NO production demonstrated that the co-administration of sub-effective doses of CA with L-NAME (the inhibitor of NOS) increased latency to seizure while decreasing nitrite levels in the PFC compared to the sub-effective dose of CA alone. Based on the results, the co-administration of an effective dose of CA with L-arg (NO precursor) did not alter latency to seizure; however, it increased nitrite levels in the PFC compared to the effective dose of CA alone.

Oxidative and nitrosative stresses can alter neurotransmission, neuronal function, and brain activity (32). The brain is rich in polyunsaturated fatty acids, making it susceptible to oxidative stress-related adaptations (33). In addition, there is a balance between the level of antioxidants and the oxidants in the brain. Under physiological conditions, the antioxidant system scavenges the basal levels of oxidative and nitrosative stress markers in the brain (34, 35). Though this stability may be disturbed under certain conditions, oxidants that exceed the antioxidant capacity can cause cellular damage (36).

NO is a transmitter that is involved in several functions in the brain. It has both physiologic and pathologic roles in the brain (37, 38). Previous research reported that NO is involved in the pathophysiology of seizures (39). In this regard, the literature indicates that seizures are associated with increased nitrite levels in brain regions involved in seizures, such as the PFC (11, 40, 41). Moreover, evidence revealed that the overproduction of NO decreased seizure threshold, though NOS inhibitors increased it (8, 42). Experimental studies indicated that the nitrite level in the PFC increased following the induction of seizure by PTZ (11). Reducing nitrite levels in the brain may serve as a promising strategy for identifying novel anticonvulsant targets. In line with previous studies, the present research confirmed that PTZ-induced seizures are associated with increased nitrite levels in the PFC.

Due to the high incidence of epilepsy in the world and regarding the low efficiency and side effects of commonly used anticonvulsants, there is a pressing need to find more effective anticonvulsants with lower side effects (43). CA (3, 4 hydroxycinnamic acid) is a polyphenolic ingredient that is abundantly found in fruits and plants

(16). It has been demonstrated that some natural compounds (e.g., CA) have neuroprotective properties (20, 23). Some previous studies reported numerous pharmacological properties, including antioxidant, anti-inflammatory, anxiolytic, and antidepressant activities, for CA (16, 44, 45). A number of studies have also shown that CA exerts neuroprotective effects across multiple models (46, 47). It has been demonstrated that CA, by modulating nitrite levels, exerts its beneficial effects in complications associated with elevated nitrite levels (48, 49). Likewise, several studies have reported that CA has anticonvulsant effects (24, 25, 50). However, the exact mechanism underlying the anticonvulsant effect of CA has not been well determined yet. Given the role of NO in the pathophysiology of seizures and the findings of some studies indicating that CA can modulate nitrite levels, this study evaluated the possible role of the nitrergic system in CA's anticonvulsant effect. The results of this interventional study showed that CA increased latency to seizure in the PTZ model in mice. Additionally, the co-administration of L-NAME (a NOS inhibitor) significantly enhanced the anticonvulsant activity of CA. Conversely, combining CA with L-arginine (a NO precursor) diminished its effect on nitrite levels in the PFC. These results indicated that the anticonvulsant effects of CA were, partially at least, mediated via the attenuation of the nitrite level in the PFC. However, more studies are warranted to confirm this association. More precisely, future studies can focus on clarifying the mechanisms underlying CA's anticonvulsant properties and assessing its safety and effectiveness. Nonetheless, our study had some limitations. It measured only nitrite levels. Thus, upcoming research should employ techniques to assess NO signaling by measuring the gene expression of NO-producing enzymes (e.g., inducible NOS, neuronal NOS, and endothelial NOS) and their protein levels. While this study focused specifically on the PFC, future investigations should also examine other brain regions in order to provide a more comprehensive understanding.

Conclusion

Based on the findings of the current study, it is evident that CA can increase latency to seizures induced by PTZ. Furthermore, an interventional study using an NOS inhibitor and a NO precursor revealed that they both potentiated and attenuated the effects of CA, respectively, indicating that nitric transmission is partly involved in the anticonvulsant effect of CA.

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Competing Interests

We have no conflict of interests to declare regarding the study described in this article and the preparation of the report.

Ethical Approval

All the experiments in this study were performed on male NMRI mice. Moreover, experiments were conducted consistent with the standards permitted by the Ethics Committee of Shahrekord University of Medical Sciences (ethical code: IR.SKUMS.REC.1398.164) and the NIH Guide for the Care and Use of Laboratory Animals (8th edition, National Academies Press). Eventually, widespread measures were taken to reduce the use of mice while improving their well-being.

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