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Antidepressant-like effect of gallic acid in mice: Dual involvement of serotonergic and catecholaminergic systems

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ABSTRACT

Aims: This study was planned to examine the antidepressant potency of gallic acid (30 and 60 mg/kg), a phenolic acid widely distributed in nature, together with its possible underlying monoaminergic mechanisms.
Main methods: Antidepressant-like activity was assessed using the tail suspension (TST) and the modified forced swimming tests (MFST). Locomotor activity was evaluated in an activity cage.
Key findings: Administration of gallic acid at 60 mg/kg reduced the immobility duration of mice in both the TST and MFST without any changes in the locomotor activity. The anti-immobility effect observed in the TST was abolished with pre-treatment of *p*-chlorophenylalanine methyl ester (an inhibitor of serotonin synthesis; 100 mg/kg i.p. administered for 4-consecutive days), ketanserin (a 5-HT2A/2C antagonist; 1 mg/kg i.p.), ondansetron (a 5-HT3 antagonist; 0.3 mg/kg i.p.), α-methyl-*para*-tyrosine methyl ester (an inhibitor of catecholamine synthesis; 100 mg/kg i.p.), phentolamine (non-selective alpha-adrenoceptor antagonist; 5 mg/kg i.p.), SCH 23390 (a dopamine D1 antagonist; 0.05 mg/kg s.c.), and sulpiride (a dopamine D2/D3 antagonist; 50 mg/kg i.p.). However, NAN 190 (a 5-HT1A antagonist; 0.5 mg/kg i.p.) and propranolol (a non-selective β-adrenoceptor antagonist; 5 mg/kg i.p.) pre-treatments were ineffective at reversing the antidepressant-like effects of gallic acid.
Significance: The results of the present study indicate that gallic acid seems to have a dual mechanism of action by increasing not only serotonin but also catecholamine levels in synaptic clefts of the central nervous system. Further alpha adrenergic, 5-HT2A/2C and 5-HT3 serotonergic, and D1, D2, and D3 dopaminergic receptors also seem to be involved in this antidepressant-like activity.

1. Introduction

Gallic acid (3,4,5-trihydroxybenzoic acid) (Fig. 1) is a naturally occurring compound widely distributed in nature as a free molecule or as a part of ester derivatives or polymers [1]. This phenolic acid has been reported to be present in fruit, seeds, leaves, bark, peel, root, or stigma of various pharmacologically active plants, such as *Acacia confusa* Merr [2]. *Ajuga bracteosa* [3], *Allium cepa* [4], *Crocus sativus* [5], *Phragmanthera austroarabica* [6], *Phyllanthus emblica* L. [7], *Psidium guajava* [8], *Terminalia catappa* Linn [9], and *Olea europaea* [10], as well as numerous foodstuffs such as raspberries, blueberries, strawberries, black and red currants, grapes (red and white wine), green and black tea, oat flour and some rice varieties [1].

To date, numerous studies have been conducted to search for possible pharmacological effects of gallic acid. So far, this phenolic acid has been demonstrated to have the following types of effects: antioxidant [5,11–13], free radical scavenging [7,13], anti-apoptotic [10], anticancer [14], chemopreventive [13,15], wound healing [16], antibacterial [17], anti-HIV [18], hepatoprotective [2], antiallergic [19], anti-inflammatory [11,13,20,21], antinociceptive [22], anti-hypertensive [23], anti-atherogenic [24], anti-colitic [25], appetite suppressant [26], anti-obesity [27–30], metabolic syndrome preventing, and antidiabetic [27,28,31–33].

Today, gallic acid has attracted a great deal of attention due to its potential efficacy in the central nervous system. Beneficial effects of this compound against neurotoxicity and neurodegeneration have been demonstrated in different experimental models, such as scopolamine-induced amnesia [34], kainic acid-induced excitotoxicity and status epilepticus [35], trimethyltin-induced hippocampal degeneration and emotional instability [36], 6-hydroxydopamine injection (full nigral lesion, animal model of Parkinson's disease)-induced memory deficit and cerebral oxidative stress [37], beta-amyloid neurotoxicity [21],

Abbreviations: AMPT, α-methyl-*para*-tyrosine methyl ester; ANOVA, one-way analysis of variance; 5-HT, serotonin; i.p., intraperitoneally; MFST, modified forced swimming test; PCPA, *p*-chlorophenylalanine methyl ester; p.o., per oral; S.E.M, standard error of mean; s.c., subcutaneously; TST, tail suspension test

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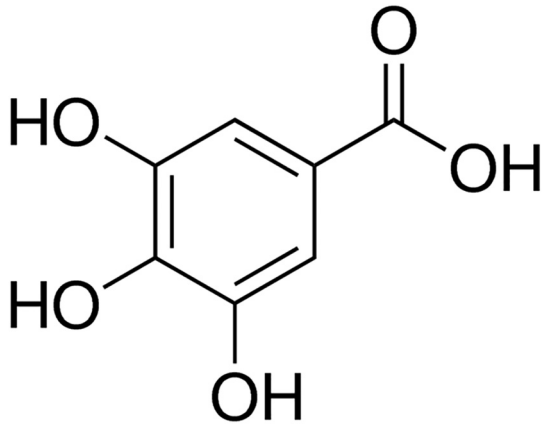

Fig. 1. Chemical structure of gallic acid.

intracerebroventricular streptozotocin injection (experimental model of sporadic Alzheimer's disease)-induced cognitive impairment and cerebral oxidative stress [38], bilateral common carotid artery occlusion-induced ischemia/reperfusion and cognitive deficits [20,39,40], and traumatic brain injury-induced behavioral, electrophysiological, and inflammatory disorders [20].

Even though there have been numerous studies reporting the neuroprotective capacity of gallic acid, only a limited number of preclinical studies have suggested a potential efficacy of this phenolic acid on emotional disorders such as anxiety [36,41–43] and depression [36,44–46]. Although antidepressant-like activity of gallic acid has been previously demonstrated by a few preclinical studies, the possible monoaminergic mechanisms underlying this effect have not yet been elucidated. Therefore, we planned to clarify the promising contributions of the serotonergic and catecholaminergic systems to the antidepressant-like effects of gallic acid in the present study.

2. Materials and methods

2.1. Animals

Tests were performed with adult male BALB/c mice, weighing 30–35 g, obtained from the Anadolu University Research Unit for Experimental Animals. Mice were housed under standard laboratory conditions. Temperature (25 ± 1 °C), light (lights on 08:00–20:00 h) and sound levels were not changed during the course of experiments. The animals had *ad libitum* access to food and water except during the test sessions. Experimental protocols and procedures of this study were approved by the Local Ethical Committee on Animal Experimentation of Anadolu University, Eskişehir, Turkey.

2.2. Drugs and administrations

α-Methyl-para-tyrosine methyl ester (AMPT), fluoxetine hydrochloride, gallic acid, NAN 190 hydrobromide, ondansetron hydrochloride, *p*-chlorophenylalanine methyl ester (PCPA), phentolamine hydrochloride, propranolol hydrochloride, reboxetine mesylate hydrate, R(+)-SCH-23390 hydrochloride, and sulpiride used in the experiments were acquired from Sigma-Aldrich (St. Louis, MO, USA), while ketanserin tartrate was purchased from Tocris Cookson (Ballwin, MO, USA).

All of the drugs, except AMPT, were dissolved in physiological saline (NaCl, 0.9%). AMPT solution was prepared using saline containing 10% Tween 80. Vehicle treatments to the appropriate control groups were carried out simultaneously.

Gallic acid (30 and 60 mg/kg by oral gavage [p.o.]) was administered three times at 24, 5, and 1 h before test sessions [47]. Reboxetine (20 mg/kg p.o.) [48] and fluoxetine (30 mg/kg p.o.) [49], conventional antidepressants, were used as positive controls. All other drugs were administered intraperitoneally (i.p.), at a volume of 10 ml/kg body weight, except SCH 23390, which was administered subcutaneously (s.c.).

2.3. Behavioral tests

2.3.1. Modified forced swimming test

The modified forced swimming test (MFST) was conducted as described previously [50]. In this test, the mice were forced to swim in a Plexiglas cylinder (height: 30 cm, diameter: 12 cm), which was filled with water to a height of 20 cm. The temperature of the water was adjusted to 25 ± 1 °C. In the "pre-test session" of the experiment, mice were allowed to swim in the cylinder for 15 min. Twenty-four h later, in the "test session", each mouse was re-exposed to the water for 5 min. Total durations of climbing (upward-directed movements with forelegs above the water level), swimming (horizontal movement on the surface of the water), and immobility (only movements necessary to keep the head above the water) behaviours over 5-s intervals were recorded. The water was changed between the individual mice to avoid the influence of alarm substances.

2.3.2. Tail suspension test

The tail suspension test (TST) was performed as described previously [51]. Briefly here, each mouse was suspended 30 cm above the floor using adhesive tape, positioned about 1 cm from the tip of the tail. The total duration of immobility, which can be defined as motionless hanging without any struggling movements, was recorded during the last 4 min of 6 min test period. Mice that climbed up their tail during the tests were excluded from the experiments.

2.3.3. Activity cage test

The locomotor activity of each mouse was assessed in an activity cage apparatus (No. 7420; Ugo Basile, Varese, Italy), containing two pairs of 16 infrared photocells 3 cm and 12 cm above the floor. Interruptions of light beams to the photocells during vertical and horizontal movements of the mouse were automatically recorded and documented for 6 min [52]. Between tests, the device was carefully cleaned with ethanol to remove any residue or odour from the former mouse.

2.4. Mechanistic studies

We additionally investigated the monoaminergic mechanisms mediating the antidepressant effect of gallic acid using various pharmacological agents. The mechanistic studies were conducted with the effective dose of 60 mg/kg.

To address the role of catecholaminergic system in the antidepressant-like effect of gallic acid, mechanistic studies were conducted with AMPT (inhibitor of tyrosine hydroxylase), phentolamine (non-selective alpha-adrenoceptor antagonist), propranolol (non-selective β-adrenoceptor antagonist), SCH 23390 (dopamine D1 receptor antagonist), and sulpiride (dopamine D2/D3 receptor antagonist). For AMPT (100 mg/kg, i.p.) studies, mice were pre-treated with AMPT or vehicle (saline with 10% Tween 80) 4 h prior the administration of physiological saline or gallic acid. Sixty min later they were tested in the TST [53,54]. For further antagonistic studies, in different experimental groups, mice were pre-treated with phentolamine (5 mg/kg, i.p.) [55], propranolol (5 mg/kg, i.p.) [56], SCH 23390 (0.05 mg/kg, s.c.) [57], sulpiride (50 mg/kg, i.p.) [58], or vehicle (saline) 15 min prior to the saline or gallic acid treatments. The TST was performed 60 min after these oral administrations of saline or gallic acid.

To investigate the probable contribution of the serotonergic system to the antidepressant-like effect of gallic acid, mechanistic studies were conducted with PCPA (inhibitor of tryptophan hydroxylase), NAN 190 (5-HT1A receptor antagonist), ketanserin (5-HT2A/2C receptor