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Agmatine attenuates stress- and lipopolysaccharide-induced fever in rats

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Abstract

Physiological stress evokes a number of responses, including a rise in body temperature, which has been suggested to be the result of an elevation in the thermoregulatory set point. This response seems to share similar mechanisms with infectious fever. The aim of the present study was to investigate the effect of agmatine on different models of stressors [(restraint and lipopolysaccaride (LPS)] on body temperature. Rats were either restrained for 4 h or injected with LPS, both of these stressors caused an increase in body temperature. While agmatine itself had no effect on body temperature, treatment with agmatine (20, 40, 80 mg/kg intraperitoneally) dose dependently inhibited stress- and LPS-induced hyperthermia. When agmatine (80 mg/kg) was administered 30 min later than LPS (500 μg/kg) it also inhibited LPS-induced hyperthermia although the effect became significant only at later time points and lower maximal response compared to simultaneous administration. To determine if the decrease in body temperature is associated with an anti-inflammatory effect of agmatine, the nitrite/nitrate levels in plasma was measured. Agmatine treatment inhibited LPS-induced production of nitrates dose dependently. As an endogenous molecule, agmatine has the capacity to inhibit stress- and LPS-induced increases in body temperature.

Keywords

Agmatine; Restraint stress; Lipopolysaccharide; Nitric oxide; Arginine; Nitrites

1. Introduction

Agmatine (l-amino-4-guanidinobutane), is an endogenous amine synthesized from the decarboxylation of arginine. Agmatine has been identified in nearly all of the organs of the rat including brain and plasma [20]. Agmatine exerts a wide range of biological activities on several organ systems, including the central nervous system, where it has been proposed to act as a neurotransmitter [22,23]. Agmatine interacts with the imidazoline receptors, alpha2-adrenoceptors, nicotinic cholinergic and 5-HT3 receptors [13,19,23]. It selectively modulates the NMDA subclass of glutamate receptors in rat hippocampal neurons [24] and has neuroprotective properties, presumably mediated by NMDA blockade [5,8,12].

Fever is an adaptive and nearly universal response among vertebrates to systemic inflammation. It is the most important non-specific systemic reaction designed to combat the

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delirious effects of invading pathogens to restore health to the afflicted host. Fever is an integrated response of the body, involving the release of endogenous pyrogens (interleukin-1, interleukin-6, tumor necrosis factor-α, etc.) by immune cells, the transfer of these immune signals to the brain, coordinated response of several brain regions to increase the thermoregulatory set point and consequently body temperature [5]. Stress-induced hyperthermia appears a consistent physiological phenomenon when organism is confronted with a stressor, either physical or psychological. Although the evoking stimuli differ, the response of the animal regarding autonomical parameters like body temperature seems to be similar. While the precise mechanism for stress-induced hyperthermia is not clear, the roles of inflammatory cytokines and NOS have been widely reported [25,30]. Agmatine has anti-depressant like effects in rat and mice models of depression [32,33] and cold immobilization stress increases endogenous production of agmatine in plasma and cortex of rats [2]. It has also been shown that agmatine suppresses the lipopolysaccharide (LPS)-induced NO production in cultured microglia [1], inducible nitric oxide synthase (iNOS) expression in macrophages and astrocytes [21] as well as in rat kidney [29]. These actions of agmatine result in the reversal low blood pressure and abnormal renal function and increases the survival after LPS treatment in mice [29].

Thus, agmatine, acting like an inhibitor of NOS and NMDA receptors, has the ability to reduce the effect of stress and inflammation. The present study was designed to investigate whether agmatine modulates the increase in body temperature after acute restraint stress and after LPS treatment and that this effect is associated with the anti-inflammatory effect of agmatine as measured by plasma nitrite/nitrate levels.

2. Materials and methods

2.1. Animals

All procedures in this study were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health (USA) and the declaration of Helsinki. Adult male Spraque Dawley rats (270–300 g) were housed in a quiet room with temperature (20±2 °C) and humidity (60±3%) control, and 12/12 h light–dark cycle was maintained (07:00–19:00 hours light). All experiments were conducted from 9 AM until the end of the experimental time period. The rats were fed standard lab chow and tap water ad lib during the study.

2.2. Measurement of body temperature

Rats from each cage were randomly numbered 1–10 (handling) 1 day prior to the temperature measurement. The temperature of all ten rats was measured sequentially by inserting a thermistor probe for a length of 4 cm into the rectum of the rat. Digital recordings of temperature were made with an accuracy of 0.1 °C by means of a Sensortek (Model BAT-12) digital thermometer. The probe, dipped into silicone oil before inserting, was held in the rectum until a stable rectal temperature was measured for 20 s. Basal temperatures were measured every 10 min for 90 min before each experiment in order to minimize the effect of handling stress on body temperature.

2.3. Restraint stress

Rats were taken out of their home cage, weighed and then colonorectal temperatures were measured. When the body temperature reached steady-state level, rat was gently placed in a Plexiglas cylinder that was designed to restrain the rat from moving or turning. Rats were remained in this position for 4 h and colonorectal temperatures were measured every 30 min until the end of the experiment.

2.4. Substances and injections

Purified lyophilized extract of *Escherichia coli* LPS and agmatine sulfate were purchased from Sigma (St. Louis, MO). LPS was dissolved in pyrogen-free 0.9% sodium chloride at a concentration of 1 mg/ml and stored −20 °C as a stock solution. On the day of experiment, LPS was diluted to 100, 200 and 500 μg/ml in saline and injected intraperitoneally. Agmatine was dissolved in pyrogen-free saline and injected (20, 40, 80 mg/kg) intraperitoneally just before LPS injection. In one experiment, agmatine was injected 30 min after LPS injection. Control rats were injected intraperitoneally with equal volume of saline. Colonorectal temperatures were recorded in all rats for 8 h. Rats were sacrificed immediately after the temperature measurements and blood was collected for the measurement of nitrite/nitrate levels.

2.5. Nitrite/nitrate determination in plasma

Trunk blood samples were collected and centrifuged at 1500 rpm for 10 min to remove red blood cells. The plasma supernatant was stored at −80 °C until analysis for nitrate using the Griess reagent. Briefly, nitrate was converted to nitrite in the presence of NADPH as enzyme cofactor and nitrate reductase. One hundred microliter of plasma was incubated for 30 min at room temperature with nitrate reductase (50 mU/100 μl sample; Sigma) and with NADPH (final concentration=80 μmol/l; Sigma) diluted in 20 mmol/l Tris buffer (pH 7.6). After incubation, samples were again centrifuged (10,000 rpm, 10 min, 4 °C) and the supernatants were used for analysis. The samples were transferred into 96-well microtiter plates, Griess reagent was added and the absorbance was measured at 540 nm using a microplate reader. Standard curve was prepared using sodium nitrite and the concentration in plasma was calculated from the standard curve.

2.6. Statistical analysis

All data are reported as means±SD. Statistical analysis of the data was made by analysis of variance (ANOVA) of repeated measures and for significance, ANOVA values were compared by Tukey's test for multiple comparisons. A probability level of less than 0.05 was accepted as significant difference.

3. Results

3.1. Effect of agmatine on body temperature

In the initial experiment, we tested whether agmatine alone had any effect on body temperature in normal rats. As shown in Fig. 1, the mean colonorectal temperature of six rats injected with saline or agmatine (80 mg/kg, i.p.). While rats disturbed by handling due to injection responded with a small increase of body temperature, this increase was slightly higher in agmatine-treated group. However, statistical analysis indicated that the observed difference was not significant.

3.2. Effect of agmatine on restraint stress-induced hyperthermia

In the second series of experiments, we tested the effect of agmatine on colonorectal temperature in rats placed in restraint tubes. Restraint stress significantly increased the body temperature that reached highest value in about 90 min (+2.5 °C) and returned to baseline levels in about 4 h (Fig. 2). The injection of 40 and 80 mg/kg doses of agmatine significantly decreased the stress-induced hyperthermia while 20 mg/kg dose was ineffective. The effect of agmatine became significant at 45 min and lasted until the end of the measurement (4 h).

3.3. Effect of agmatine on LPS-induced temperature increase

Following the effects on stress, we investigated whether agmatine would exhibit similar anti-pyretic effects after the administration of LPS, the bacterial endotoxin. Intraperitoneal administration of LPS (100, 200 and 500 μg/kg) increased the body temperature dose dependently (Fig. 3). While the temperature tend to return to control levels after 7 h with 100 and 200 μg/kg doses, the higher dose resulted in prolonged increase in body temperature that returned to baseline levels only after 24 h. Agmatine (20, 40, 80 mg/kg), administered with high dose of LPS (500 μg/kg), significantly reduced the increase in body temperature beginning at 45 min after injection (Fig. 4). To determine whether the effect of agmatine is related to initial peripheral activation of immune system by LPS, we assessed the effect of agmatine, administered 30 min after LPS injection. As shown in Fig. 5, the effect of delayed administration of agmatine (80 mg/kg) was not exactly the same as co-administration. For example, the decrease in body temperature after LPS administration became significant only after about 120 min (compared to 30 min in co-administration). Moreover, the maximal effect at 420 min was a decrease of about 1.5 °C from LPS only treatment and this effect was significantly lower ($P < 0.05$) compared to co-administration experiment where the decrease was about 2.0 °C (Fig. 3).

3.4. Effect of agmatine on LPS-induced nitrite production

One of the widely studied markers of inflammation during LPS exposure is the activation of NOS and increase in blood nitrite levels. We tested whether the anti-pyretic effects of agmatine were associated with lower immune response to LPS as measured by blood nitrite/nitrate levels. LPS (500 μg/kg) significantly increased nitrite/nitrate levels in rat plasma at 8 h from about 50 μM in control rats to about 350 μM after LPS treatment. Agmatine at all three doses (20, 40 and 80 mg/kg) significantly reduced the increase in nitrite/nitrate with levels returning to almost control values at highest dose of agmatine (Fig. 6).

4. Discussion

In this study, we report that agmatine significantly reduces the increase in body temperature induced by acute restraint stress and bacterial endotoxin, LPS. Several previous studies have reported the effects of agmatine in reducing inflammatory response. Agmatine reduces spinal nociceptive reflex [3], neuropathic pain [16,17], thermal hyperalgesia induced by inflammation [10] and pain induced by inflammation [5] in different animal models. These effects were observed in agmatine doses ranging from 10 to 100 mg/kg without any behavioral/cardiovascular effects in naïve animals. We observed significant effect on stress and LPS-induced increase in body temperature at lower dose of 20 mg/kg. The plasma level of agmatine is relatively low (6.1±1.1 ng/ml) in normal rats but increases to much higher levels (50±9 ng/ml) after cold–restraint stress [2]. The biosynthesis of agmatine also increases in pathological conditions such as inflammation (kidney) [7,27] and ischemia (brain)[6].

Stress-induced hyperthermia appears to be a consistent physiological phenomenon when organism is confronted with a stressor, either physical or psychological. While the precise mechanism for stress-induced hyperthermia is not clear, the roles of inflammatory cytokines and NOS have been widely reported in thermoregulation [4,25,30]. In our previous study, we showed that restraint/cold stress caused a large increase in plasma agmatine levels whereas restraint stress alone had no effect [2]. In present study, we have observed that restraint stress induced increase in body temperature was inhibited by agmatine in a dose dependent manner. Thus, agmatine appears to be involved in neuroendocrine regulation during stress response. Agmatine has anti-depressant like effects in rat and mice models of depression [32,33]. Recently, we have shown that cold–restraint stress increases endogenous

production of agmatine in plasma and cortex of rats [2]. The plasma levels of agmatine has been found to be increased in depressed patients [9]. It has been shown that agmatine may modulate memory and other behavioral functions, since it produces an amnesic effect when administered before fear conditioning [16]. The facts that several nuclei of hypothalamus have highest agmatine immunoreactivity [9,18] and that agmatine may be co-localized with neuropeptide in hypothalamus and posterior pituitary [31] further suggest a role for agmatine in stress response.

To determine whether the anti-hyperthermic effect of agmatine is mediated by central action, we investigated the effect of agmatine on hyperthermia induced by peripheral administration of LPS. Fever is an adaptive response to systemic infection and is an integrated response of the body, involving the release of endogenous pyrogens (interleukin-1, interleukin-6, tumor necrosis factor-α, etc.) by peripheral immune cells [4]. The transfer of these immune signals to the brain results in coordinated response of several brain regions to increase the thermoregulatory set point and body temperature [25]. While the initial events may be different, the common link in stress and LPS-induced increase in body temperature is the production/release of pro-inflammatory cytokines. When LPS and agmatine are administered together, agmatine significantly attenuated LPS-induced hyperthermia and nitrate production. While the action of agmatine could be mediated by central or peripheral mechanisms, the findings from the delayed administration of agmatine have suggested both possibilities. If agmatine is acting only centrally, then the effect of co-administration should be same as late administration. In contrast, if agmatine is inhibiting only the peripheral immune response to LPS, then the late administration should not have any significant effect. We have observed that the late administration of agmatine suppressed the LPS-induced hyperthermia although with some delay and with lower maximal response. This would suggest that agmatine may be acting both peripherally (inhibiting initial immune activation) as well as centrally to lower the body temperature after LPS injection.

Previously it has been shown that agmatine attenuates iNOS mediated NO generation if administered prior to, during or after administration of cytokines in vivo and in vitro [15,21,29]. It has been shown that agmatine (50 mg/kg i.p.) increased the survival of LPS treated mice administered with a high dose of LPS (10 mg/kg i.p.) [29]. Moreover, agmatine prevented the decreases in blood pressure and renal function normally associated with endotoxic shock [15,29]. All these earlier findings along with our present data suggest that agmatine has peripheral anti-inflammatory effects.

As an intracellular metabolite of arginine, agmatine modulates the production of polyamines and nitric oxide synthesis [1,11,21,28]. Agmatine inhibits the cell growth by reducing polyamine production [28] and suppresses the expression of iNOS after inflammatory stimulation [1,21]. There are also reports demonstrating the changes in the production of endogenous agmatine after inflammatory stimulation. For example, the activity of arginine decarboxylase and the levels of agmatine are increased shortly after LPS injection in kidney in vivo [14] and in cultured macrophages in vitro [21,26], providing evidence for the role of endogenous agmatine during systemic infection.

In conclusion, while agmatine itself had no effect on body temperature, it attenuates both stress- and LPS-induced hyperthermia. As agmatine also inhibited LPS-induced nitrite production, this effect may be mediated by its peripheral anti-inflammatory actions although the action at central hypothalamic peptides especially during stress cannot be ruled out at this time. These findings support the hypothesis that agmatine may be an endogenous anti-inflammatory molecules whose synthesis and release may be regulated in response to stress and inflammation.

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References

1. Abe K, Abe Y, Saito H. Agmatine suppresses nitric oxide production in microglia. Brain Res. 2000; 872:141–8. [PubMed: 10924686]
2. Aricioglu F, Regunathan S, Piletz JE. Is agmatine an endogenous factor against stress? Ann N Y Acad Sci. 2003; 1009:136–40. [PubMed: 15028578]
3. Bradley KJ. Effect of agmatine on spinal nociceptive reflexes: lack of interaction with alpha2-adrenoceptor or mu-opioid receptor mechanisms. Eur J Pharmacol. 1997; 331:133–8. [PubMed: 9274971]
4. Dinarello CA. The proinflammatory cytokines interleukin-1 and tumor necrosis factor and treatment of septic shock syndrome. J Infect Dis. 1991; 163:1177–84. [PubMed: 2037782]
5. Fairbanks CA, Schreiber KL, Brewer KL, Yu CG, Stone LS, Kitto KF, et al. Agmatine reverses pain induced by inflammation, neuropathy, and spinal cord injury. Proc Natl Acad Sci U S A. 2000; 97:10584–9. [PubMed: 10984543]
6. Feng Y, Piletz JE, Leblanc MH. Agmatine suppresses nitric oxide production and attenuates hypoxic–ischemic brain injury in neonatal rats. Pediatr Res. 2002; 52:606–11. [PubMed: 12357058]
7. Gaillet S, Malaval F, Barbanel G, Pelletier G, Assenmacher I, Szafarczyk A. Inhibitory interactions between alpha 2-adrenergic and opioid but not npy mechanisms controlling the crf–acth axis in the rat. Regul Pept. 1991; 36:249–61. [PubMed: 1666688]
8. Gilad GM, Salame K, Rabey JM, Gilad VH. Agmatine treatment is neuroprotective in rodent brain injury models. Life Sci. 1996; 58:PL41–6.
9. Gorbatyuk OS, Milner TA, Wang G, Reis DJ, Ragunathan S. Localization of agmatine in vasopressin and oxytocin neurons of the rat hypothalamic paraventricular and supraoptic nuclei. Exp Neurol. 2002; 171:235–45. [PubMed: 11573976]
10. Horvath G, Kekesi G, DI, Szikszay M, Klimscha W, Benedek G. Effect of intrathecal agmatine on inflammation-induced thermal hyperalgesia in rats. Eur J Pharmacol. 1999; 368:197–204. [PubMed: 10193655]
11. Ishizuka S, Cunard R, Poucell-Hatton S, Wead L, Lortie M, Thomson SC, et al. Agmatine inhibits cell proliferation and improves renal function in anti-thy-1 glomerulonephritis. J Am Soc Nephrol. 2000; 11:2256–64. [PubMed: 11095648]
12. Kim JH, Yenari MA, Giffard RG, Cho SW, Park KA, Lee JE. Agmatine reduces infarct area in a mouse model of transient focal cerebral ischemia and protects cultured neurons from ischemia-like injury. Exp Neurol. 2004; 189:122–30. [PubMed: 15296842]
13. Loring RH. Agmatine acts as an antagonist of neuronal nicotinic receptors. Br J Pharmacol. 1990; 99:207–11. [PubMed: 2331571]
14. Lortie MJ, Ishizuka S, Schwartz D, Blantz RC. Bioactive products of arginine in sepsis: tissue and plasma composition after LPS and iNOS blockade. Am J Physiol, Cell Physiol. 2000; 278:C1191–9. [PubMed: 10837347]
15. Lortie MJ, Novotny WF, Peterson OW, Vallon V, Malvey K, Mendonca M, et al. Agmatine, a bioactive metabolite of arginine. J Clin Invest. 1996; 97:413–20. [PubMed: 8567962]
16. Onal A, Delen Y, Ulker S, Soykan N. Agmatine attenuates neuropathic pain in rats: possible mediation of nitric oxide and noradrenergic activity in the brainstem and cerebellum. Life Sci. 2004; 73:413–28. [PubMed: 12759136]
17. Onal A, Soykan N. Agmatine produces antinociception in tonic pain in mice. Pharmacol Biochem Behav. 2001; 69:93–7. [PubMed: 11420073]
18. Otake K, Ruggiero DA, Regunathan S, Wang H, Milner TA, Reis DJ. Regional localization of agmatine in the rat brain: an immunocytochemical study. Brain Res. 1998; 787:1–14. [PubMed: 9518530]

19. Piletz JE, Chikkala DN, Ernsberger P. Comparison of the properties of agmatine and endogenous clonidine-displacing substance at imidazoline and alpha-2 adrenergic receptors. J Pharmacol Exp Ther. 1995; 272:581–7. [PubMed: 7853171]
20. Raasch W, Regunathan S, Li G, Reis DJ. Agmatine, the bacterial amine, is widely distributed in mammalian tissues. Life Sci. 1995; 56:2319–30. [PubMed: 7791519]
21. Regunathan S, Piletz JE. Regulation of inducible nitric oxide synthase and agmatine synthesis in macrophages and astrocytes. Ann N Y Acad Sci. 2003; 1009:20–9. [PubMed: 15028566]
22. Regunathan S, Reis DJ. Imidazoline receptors and their endogenous ligands. Ann Rev Pharmacol Toxicol. 1996; 36:511–44. [PubMed: 8725400]
23. Reis DJ, Regunathan S. Is agmatine a novel neurotransmitter in brain? Trends Pharmacol Sci. 2000; 21:187–93. [PubMed: 10785653]
24. Reis DJ, Yang XC, Milner TA. Agmatine containing axon terminals in rat hippocampus form synapses on pyramidal cells. Neurosci Lett. 1998; 250:185–8. [PubMed: 9708863]
25. Roth J, de Souza GEP. Fever induction pathways: evidence from responses to systemic or local cytokine formation. Braz J Med Biol Res. 2001; 34:301–14. [PubMed: 11262580]
26. Sastre M, Galea E, Reis DJ, Ragunathan S. Metabolism of agmatine in macrophages: modulation by lipopolysaccharides and inhibitory cytokines. Biochem J. 1998; 330:1405–9. [PubMed: 9494113]
27. Satriano J. Arginine pathways and the inflammatory response: interregulation of nitric oxide and polyamines: review article. Amino Acids. 2004; 26:321–9. [PubMed: 15290337]
28. Satriano J, Matsufuji S, Murakami Y, Lortie MJ, Schwartz D, Kelly CJ, et al. Agmatine suppresses proliferation by frameshift induction of antienzyme and attenuation of cellular polyamine levels. J Biol Chem. 1998; 273:15313–6. [PubMed: 9624108]
29. Satriano J, Schwartz, Ishizuka M, Lortie M, Thomson SC, Gabbai FB, et al. Suppression of inducible nitric oxide generation by agmatine aldehyde: beneficial effects in sepsis. J Cell Physiol. 2001
30. Steiner AA, Branco LGS. Nitric oxide in the regulation of body temperature and fever. J Therm Biol. 2001; 26:325–30.
31. Wang G, Gorbatyuk O, Dayanithi G, Ouyang W, Wang J, Milner TA, et al. Evidence for endogenous agmatine in hypothalamo-neurohypophysial tract and its modulation on vasopressin release and Ca2+ channels. Brain Res. 2002; 932:25–36. [PubMed: 11911858]
32. Zomkowski AD, Oscar Rosa A, Lin J, Santos AR, Batista Calixto J, Lucia Severo Rodrigues A. Evidence for serotonin receptor subtypes involvement in agmatine antidepressant like-effect in the mouse forced swimming test. Brain Res. 2004; 1023:253–63. [PubMed: 15374751]
33. Zomkowski AD, Hammes L, Calixto JB, Lin J, Santos AR, Rodrigues AL. Agmatine produces antidepressant-like effects in two models of depression in mice. Neuroreport. 2002; 13:387–91. [PubMed: 11930146]

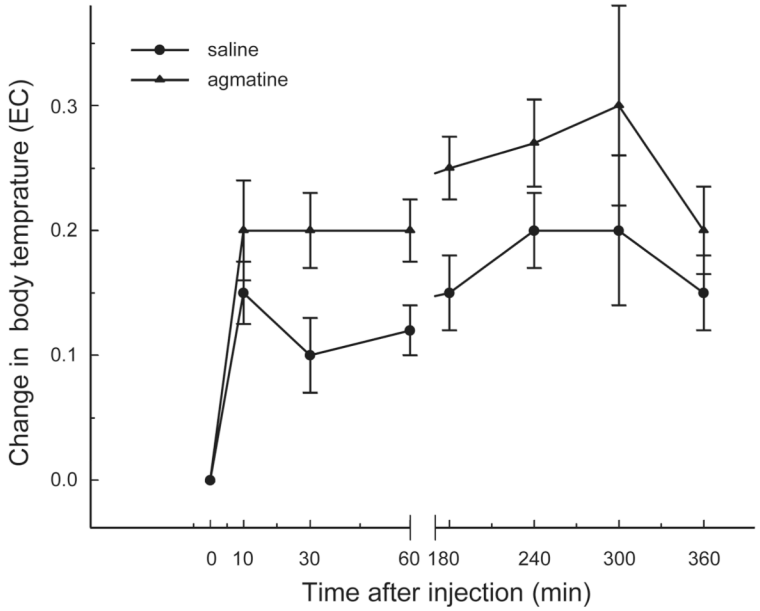

Fig. 1.

Effect of agmatine on body temperature. Changes in body temperature over time was measured in rats injected intraperitoneally with agmatine (80 mg/kg) or saline in freely moving rats. Values are means±SE from six animals in each group.

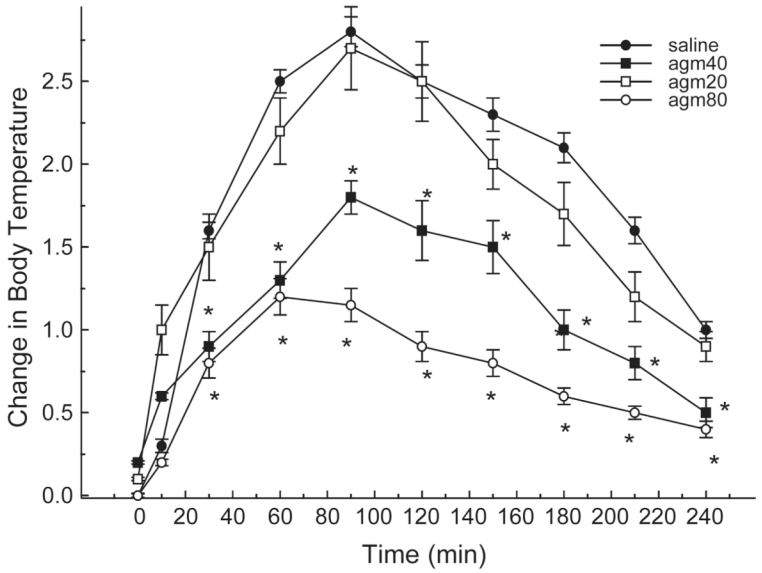

Fig. 2.

Effect of agmatine on body temperature in acutely restrained rats. Changes in body temperature over time was measured in rats injected intraperitoneally either with saline or agmatine (20, 40, 80 mg/kg) in restraint stress cage. Data presented as means±SE from six animals in each group. **P* <0.05 compared to saline group.

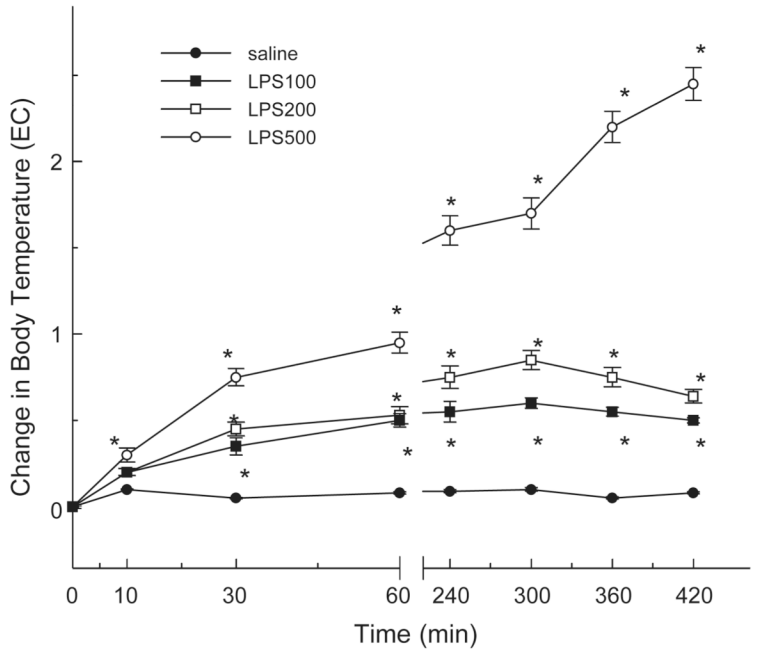

Fig. 3.

Effect of LPS on body temperature in rats. Body temperature was measured in rats injected intraperitoneally with different doses of LPS (100, 200 and 500 μg/kg) or saline. Data presented as means±SE from six animals in each group. **P* <0.05 compared to saline group.

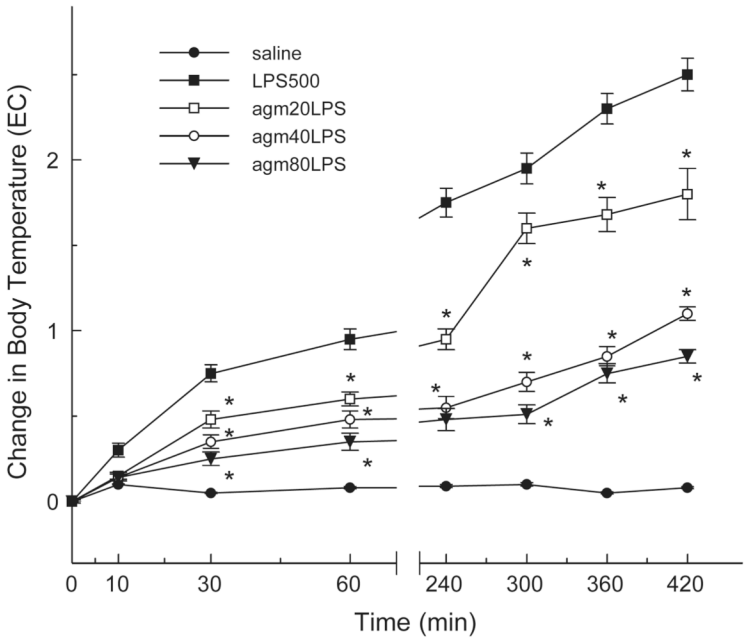

Fig. 4.

Effect of agmatine on increase in body temperature induced by LPS. Agmatine (20, 40, 80 mg/kg) and LPS (500 μg/kg) were injected together and body temperature was measured for 7 h. Values are means±SE from six animals in each group. **P* <0.05 compared to LPS group. Values in LPS-treated groups, starting at 30 min, were significantly different (*P* <0.05) compared to corresponding time point in saline group.

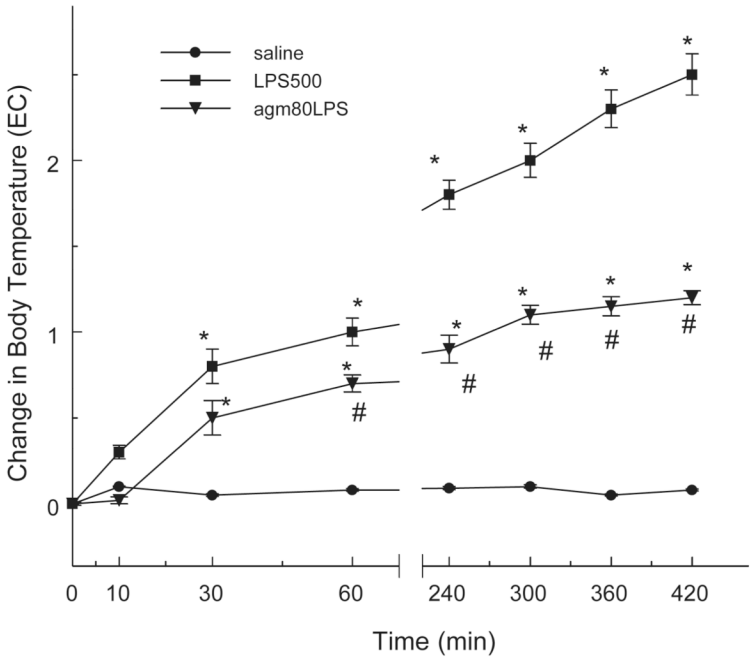

Fig. 5.

Effect of delayed administration of agmatine on body temperature. Agmatine (80 mg/kg) was injected 30 min after LPS (500 μg/kg) injection and body temperature was measured for 7 h. Values are means±SE from six animals in each group. **P* <0.05 compared to saline group; #*P* <0.05 compared to LPS group.

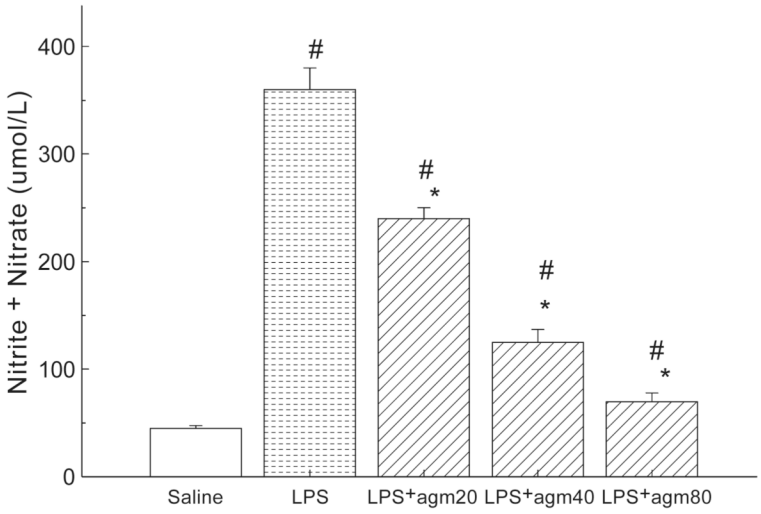

Fig. 6.

Effect of agmatine on plasma total nitrite/nitrate levels. Agmatine (20, 40, 80 mg/kg) was injected along with LPS (500 μg/kg) injection and plasma nitrite/nitrate levels were measure after 7 h. Values are means±SE from six animals in each group. **P* <0.05 compared to LPS group; $^{\#}P$ <0.05 compared to saline group.