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Адрес на редакцията
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ул. "Дунав" 2, София 1000
Факс (02) 987 987 4
Гл. редакпор: ✆ (02) 987 987 4
E-mail:snikolov@mbox.pharmfac.acad.bg

Address of Editorial Board
Faculty of Pharmacy
2, Dunav str., Sofia 1000
Fax (02) 987 987 4
Editor in Chief: ✆ (+359 2) 987 987 4
E-mail:snikolov@mbox.pharmfac.acad.bg

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EFFECT OF CAFFEINE ON BODY TEMPERATURE OF RATS IN NORM AND DEPRESSION

R. Nikolov[1], Y. Chekalarova[2], D. Pehlivanova[2], L. Tancheva[2], V. V. Petkov[2] and K. Yakimova[1]
[1]Department of Pharmacology and Toxicology, Medical Faculty, Medical University – Sofia
[2]Institute of Neurobiology, Bulgarian Academy of Sciences

Summary. Main pharmacological effects of caffeine are mediated by its blockade of adenosine receptors. Recent experimental data suggest involvement of purinergic mechanisms in the regulation of body temperature. The present study determined the effects of caffeine on the core body temperature in rats at ambient temperature of 22 ± 1ºC. We investigated the changes of core body temperature in male Wistar rats after systemic (i.p.) administration of caffeine on the two experimental animal groups: (1) normal rats; (2) rats with experimental model of depression. Lower doses of caffeine (2, 20 and 40 mg/kg) produced a significant and dose-dependent rise of body temperature in rats from both experimental groups. The hyperthermic effect in normal rats was observed soon after application of caffeine and lasted about 90 min. The hyperthermic effect in rats with experimental model of depression was also observed soon after application of caffeine and lasted about 150 min. High dose of caffeine (100 mg/kg) induced significant hypothermia between 90th and 150th min in normal rats and hyperthermia between 30th and 60th min in rats with experimental model of depression.

Key words: body temperature, caffeine, hyperthermia, hypothermia, rats

ЕФЕКТИ НА КОФЕИНА ВЪРХУ ТЕЛЕСНАТА ТЕМПЕРАТУРА НА ПЛЪХОВЕ ПРИ НОРМА И ДЕПРЕСИЯ

Р. Николов[1], Я. Чекаларова[2], Д. Пехливанова[2], Л. Танчева[2], В. В. Петков[2] и К. Якимова[1]
[1]Катедра по фармакология и токсикология, Медицински факултет, Медицински университет – София
[2]Институт по невробиология, БАН

Резюме. Основните фармакологични ефекти на кофеина се осъществяват посредством блокиране на аденозиновите рецептори. Съвременни експериментални изследвания предполагат участието на пуринергични механизми в регулацията на телесната температура. В настоящото проучване е изследван ефектът на кофеин върху телесната температура на плъхове при лабораторна температура (22 ± 1ºC). Проучихме промяната в телесната температура на мъжки плъхове от порода Wistar след системно (интраперитонеално) приложение на кофеин при две експериментални групи животни: (1) нормални плъхове; (2) плъхове с експериментален модел на депресия. Прилагането на кофеин в по-ниски дози (2, 20 и 40 mg/kg) предизвика дозозависимо покачване на телесната температура на плъховете и от двете експериментални групи. Хипертермичният ефект, наблюдаван при нормалните плъхове, се прояви скоро след инжектирането на кофеина и продължи 90 min. Хипертермичният ефект, наблюдаван при плъховете от групата с експериментален модел на депресия, се прояви скоро след инжектирането на кофеина и продължи 150 min. Прилагането на кофеин във високи дози (100 mg/kg) предизвика значима хипотермия между 90-ата и 150-ата минута при нормалните плъхове и хипертермия между 30-ата и 60-ата минута при плъховете от групата с експериментален модел на депресия.

Ключови думи: телесна температура, кофеин, хипертермия, хипотермия, плъхове

Introduction

Thermoregulation in mammals is a complex physiologic process that serves to maintain core temperature at a constant set point (for humans, the set point in health is 37 ± 0,4°C, while in other mammals set point has a range of 36-38°C). The thermoregulatory center resides in the preoptic area of the anterior hypothalamus (PO/AH) and controls the balance between heat gain and heat loss (Boulant, 2000). Drugs that affect acetylcholine,

norepinephrine, dopamine, and serotonin neurotransmission are associated with various hyperthermic syndromes. The effects on body temperature of morphine and other μ-receptor agonists are biphasic in rats and mice, with low doses producing hyperthermia and higher doses resulting in hypothermia (Rosow et al., 1980; Geller et al., 1983). Many experimental data and our previous studies showed that direct or indirect GABA-acting drugs produce dose-dependent hypothermia in conscious rats.

Recent literature data reported involvement of purinergic signaling in central mechanisms of body temperature regulation in rats (Gourine et al., 2002). Adenosine acts as modulator, which produces many pharmacological effects, both in the periphery and in the CNS (Brundege and Dunwiddie, 1997; Dunwiddie and Masino, 2001; Fredholm et al., 2005). More important adenosine antagonists are methylxanthines theophylline and caffeine. Caffeine is most widely used psychoactive drug. Pharmacological action of caffeine includes stimulation of the central nervous system, cardiac muscle, voluntary muscles, acid secretion, and diuresis. Caffeine increases alertness, reduces fatigue, and can elevate mood (Smith, 2002). The psychological effects of caffeine are dose-related. Lower doses produce stimulation of CNS, which is often perceived as desirable, whereas higher doses can cause caffeinism (Daly and Fredholm, 1998; Rogers and Dernoncourt, 1997).

Systemic administration of adenosine lowered rectal temperature in rats, but co-administration of caffeine and adenosine reversed hypothermic effect of adenosine (Wager-Srdar et al, 1983). Experimental data showed influence of theophylline and caffeine on thermoregulatory functions of rats (Lin et al., 1980; Durcan and Morgan, 1991; Zarrindast and Heidari, 1994).

The aim of the present study was to investigate the effects of caffeine on the core body temperature in normal rats, as well as in rats with experimental model of depression.

Materials and methods

Substances. Caffeine Reagent Plus (Sigma, Germany) was used in this study. The doses used were defined by literature data, as well as own previously experiments. The substances were administered systemic (intraperitoneally, i.p.) in a volume 0,5 ml/100 g body weight.

Experimental animals. The experiments were carried out on male Wistar rats (weight range 200-250 g), divided into groups of 6-8 rats each. Animals were maintained on a standard 12 h light/dark cycle and allowed food and water ad libitum. All experiments started at 10 a.m. and were conducted at ambient temperature 22 ± 1°C. In the handling and care of all animals, the International Guiding Principles for Animal Research were strictly followed.

Depression model. Animals were exposed to various stress acting factors during 30 days, when the positive tests of depression developing were observed.

Monitoring of body temperature. Temperature was measured with thermistor probes (TX8) inserted rectally to a depth of 6 cm and monitored on multichannel recorder Iso-Thermex 16 (Columbus Instruments, USA). The initial temperature of the animals was determined, and then checked at 30-min intervals until the end of the effect observed. The movements of the rats were slightly restricted, as previously described by Rosow et al. (1980).

Data analysis. The results were expressed as delta (Δ) values (average changes in temperature compared to the initial one) (mean Δ values ± S.E.M.) and analyzed with two-way analysis of variance. For statistical significance a Student's t-test was used.

Results

1. Effects of caffeine on the core body temperature in normal rats.

Systemic (i.p.) administration of caffeine in lower doses (2, 20 and 40 mg/kg) caused a dose-dependent increase in body temperature in normal rats with a maximum response on the 60^{th} min after drug application. Caffeine (2, 20 and 40 mg/kg) i.p. produced significant hyperthermia that occurred at 30, 60 and 90^{th} min after application (Fig.1).

Injection of caffeine in a high dose (100 mg/kg) i.p. caused significant decrease in core body temperature in normal rats between 90th and 150th min ($P < 0,05$). The hypohermia was developed slowly, with maximum response on the 120th min after application (Fig. 2).

2. Effects of intraperitoneal (i.p.) injection of caffeine on the core body temperature in rats with experimental model of depression.

Administration of caffeine in low doses (2, 20 and 40 mg/kg) i.p. caused a significant and long lasting increase in core body temperature in rats with experimental model of depression. The hyperthermia was developed soon after drug administra-

tion, with maximum response on the 60th min and continuance until 150th min (Fig. 3). There was a trend of increasing of the hyperthermia in rats with experimental model of depression in comparison with normal rats, but this trend was not significant.

Injection of caffeine in a dose of 100 mg/kg i.p. induced increase in core body temperature in rats with experimental model of depression observed at 30th and 60th min after drug application ($P < 0,05$) (Fig. 4).

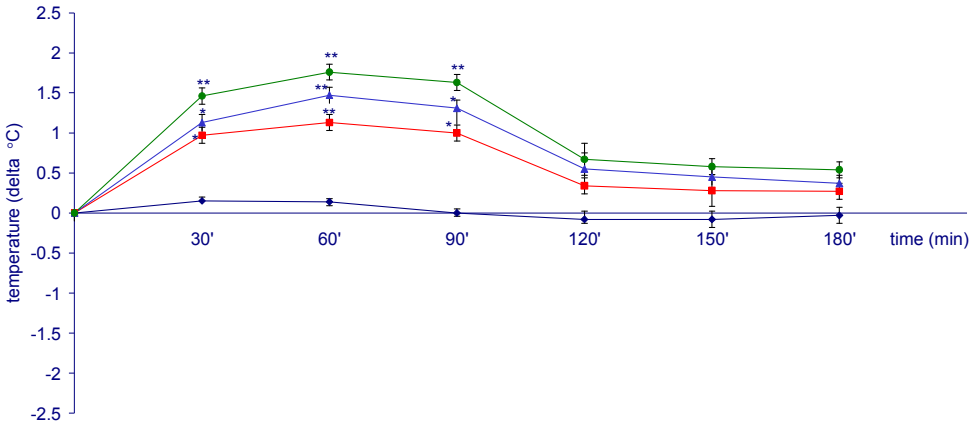

Fig. 1. *Effect of intraperitoneal application (i.p.) of caffeine (lower doses) on body temperature in normal rats*
Mean change (temperature delta °C) after i.p. administration of ■ caffeine 2 mg/kg, ▲ caffeine 20 mg/kg, ● caffeine 40 mg/kg and ◆ NaCl (control). Significant differences: *P < 0,05, **P < 0,01

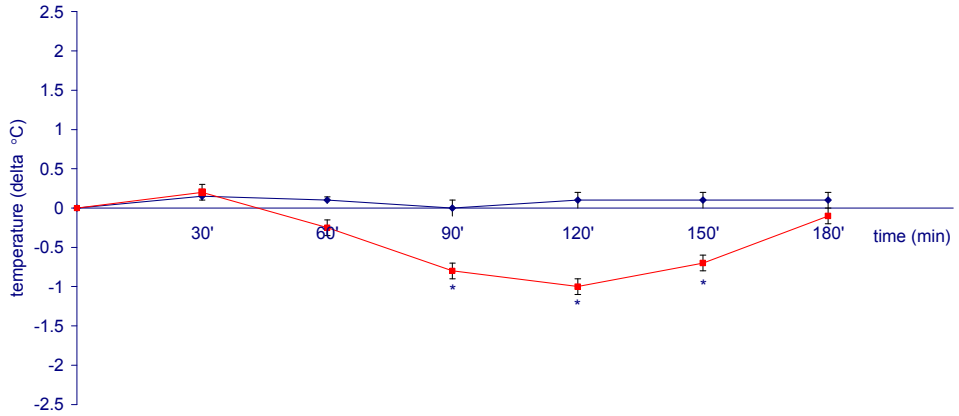

Fig. 2. *Effect of intraperitoneal application (i.p.) of caffeine (high dose) on body temperature in normal rats*
Mean change (temperature delta °C) after i.p. administration of ■ caffeine 100 mg/kg, and ◆ NaCl (control). Significant differences: *P < 0,05

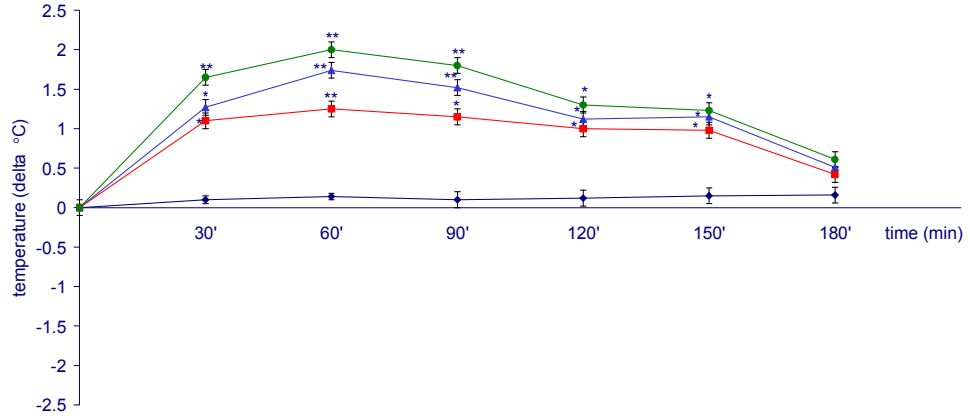

Fig. 3. *Effect of intraperitoneal application (i.p.) of caffeine (lower doses) on body temperature in rats with experimental model of depression*
Mean change (temperature delta °C) after i.p. administration of ■ caffeine 2 mg/kg, ▲ caffeine 20 mg/kg, ● caffeine 40 mg/kg and ◆ NaCl (control). Significant differences: *P < 0,05, **P < 0,01

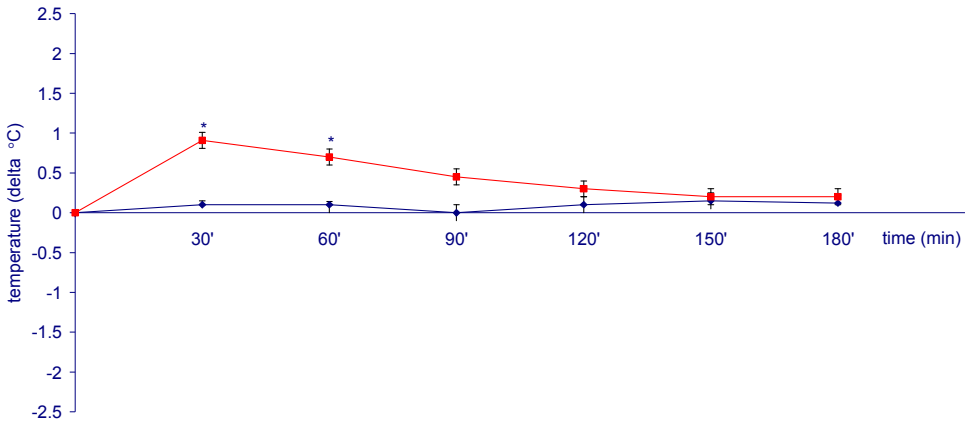

Fig. 4. *Effect of intraperitoneal application (i.p.) of caffeine (high dose) on body temperature in rats with experimental model of depression*

Mean change (temperature delta °C) after i.p. administration of ■ caffeine 100 mg/kg, and ◆ NaCl (control). Significant differences: *P < 0,05

Discussion

Our results suggest that effects of caffeine on core body temperature in rats are dose-related. Systemic administration of lower doses of caffeine produces significant dose-dependent hyperthermia in normal rats, as well as in rats with experimental model of depression. However, high dose of caffeine induces slowly developed fall in body temperature in normal rats, while high dose of caffeine causes short lasting increase in body temperature in rats with experimental model of depression.

It has been reported that acute administration of adenosine antagonist caffeine produced dose-dependent changes in the body temperature of rats (Schlosberg, 1983; Wager-Srdar et al, 1983). The pharmacological effects of caffeine are mediated by three basic cellular actions: (1) adenosine receptor blockade; (2) increasing accumulation of cyclic nucleotides by inhibition of phosphodiesterases; (3) release of intracellular calcium. Caffeine is a non-selective adenosine receptor antagonist, with reported similar in vitro affinities for A1, A2A and A2B receptors and with lower affinity for A3 receptors (Ferre, 2008). A2 adenosine receptors are present in hypothalamic and brainstem nuclei involved in the regulation of body temperature (Gourine et al., 2002).

Probably, the thermoregulatory effects of caffeine are mediated through interaction between purinergic system and other central neurotransmitters or neuromodulators involved in thermoregulation, such as serotonin, norepinephrine, dopamine, acetylcholine, β-endorphin. Co-administration of caffeine with substituted amphetamines (MDMA, MDA) promotes hyperthermia and serotonin loss (McNamara et al., 2006). Hyperthemia induced by caffeine can occur from behavioral excitation via release of catecholamines leading to an increased metabolism (Lin et al., 1980). Opioid receptors may play a role in hypothermic effect of caffeine. Pretreatment with opioid receptor antagonist naloxone attenuated hypothermic action of caffeine (Durcan and Morgan, 1992). Caffeine enhances oxygen consumption that may reflect a stimulation of caffeine on brown adipose tissue thermogenesis (Wellman and Marmon, 1985).

Our results suggest that hyperthermic reaction of caffeine is prolonged in rats with experimental model of depression. In many species, psychological stress causes rise in core body temperature (Briese and De Quijada, 1970; Snow and Horita, 1982; Zethof et al., 1994). Stress-induced hyperthermia in animals is commonly called psychological stress-induced rise in core temperature (PSRCT) or so-called ”psychogenic fever” in humans. The stress-induced rise in core temperature is a fever (rise in the thermoregulatory set point) and may occur through prostaglandin E_2-dependent mechanisms or 5-HT-mediated mechanisms (Oka et al., 2001).

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✉ **Address for correspondence:**
Prof. Dr. Krassimira S. Yakimova
Department of Pharmacology and Toxicology
Faculty of Medicine
Medical University
2 Zdrave Str.
1431 Sofia
Bulgaria
e-mail: kyakim@medfac.acad.bg
e-mail: kyakimova@yahoo.com

✉ **Адрес за кореспонденция:**
Проф. д-р Красимира С. Якимова
Катедра по фармакология и токсикология
Медицински факултет
Медицински университет
ул. "Здраве" № 2
1431 София
България
e-mail: kyakim@medfac.acad.bg
e-mail: kyakimova@yahoo.com