EVIDENCE FOR THE INVOLVEMENT OF EICOSANOIDS IN REGULATION OF NORMAL BODY TEMPERATURE

V. Fraifeld[1], L. Paul[1], J. Kaplanski[1], W. Kozak[2] and M.J. Kluger[2], [1]Dept of Clinical Pharmacology, Ben-Gurion University of the Negev, Israel and [2]Dept of Physiology, Medical College of Georgia, Augusta, GA, USA.

A regulated rise in the thermoregulatory set point has been postulated to be responsible for both fever and circadian elevation of body temperature (T_b). Consequently, in view of the fever-inducing role of prostaglandin E_2 (PGE_2), it was suggested that this rise could be prostaglandin-dependent. In support of this are data demonstrating that the normal nighttime rise in T_b of rats can be prevented by antipyretic drugs known as cyclooxygenase inhibitors (Scales and Kluger, 1987). However, circadian changes in hypothalamic PGE_2 production have not yet been established. We have recently shown that 5-lipoxygenase (Paul *et al.*, 1999; Fraifeld *et al.*, 2000) and cytochrome P-450 (Kozak *et al.*, 1998; 2000) pathways of arachidonate metabolism are involved in the process of endogenous antipyresis (cryogenesis) during response to endotoxin. Whether lipoxygenase- and epoxygenase-derived eicosanoids are also involved in the regulation of normal T_b is unknown. The experiments were carried out on conscious young adult male CD-1 mice and Sprague-Dawley rats maintained at 12:12-h light/dark photoperiods. T_b was recorded either biotelemetrically or by using a rectal probe. PGE_2 production by *ex-vivo* incubated hypothalamus was measured before and after the onset of dark. The hypothalami were excised after decapitation. The inhibitors of different metabolic pathways of arachidonic acid cascade were injected intraperitoneally (ip). Intra-abdominal implantation of temperature-sensitive transmitters and intracerebral implantation of a guide cannula were performed in mice anaesthetized with ketamine (80 mg/kg, ip) and xylazine (16 mg/kg, ip). It was found that (i) dark-induced elevation in T_b of mice and rats was accompanied by a significant increase in hypothalamic PGE_2 production (by 71 and 60%, respectively); (ii) indomethacin at a dose (5 mg/kg, ip) that did not affect the daytime values of T_b, prevented the increase in T_b after the onset of dark; (iii) the T_b of CD-1 mice tended to decrease during the light period, reaching the minimum values between 12:00 to 14:00. This decrease was significantly reduced by pretreatment of mice with the inhibitor of leukotriene (LT) synthesis MK-886 (1 mg/kg, ip); (iv) injection of 0.3 nmol LTC_4 into the lateral ventricle, which caused a drop in T_b of CD-1 mice by ~1.6°C during the light phase, significantly reduced the nighttime rise in T_b. The results presented support a role of PGE_2 and leukotrienes in the regulation of normal daily variations of T_b, which occurs in a similar fashion as during fever.

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vadimfra@zahav.net.il