Intracerebroventricular administration of Hemin elicits febrile response

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It is widely accepted that inflammation and exogenous pyrogens evoke fever through the activation of macrophages to release endogenous pyrogenic cytokines (IL-1β, IL-6 and TNF-α) and the ending step in febrile response is the action of a PGE2 on thermoregulatory pathways in the hypothalamus. However, the precise mechanism by which blood-borne cytokines increase PGE2 synthesis in hypothalamus is still unclear. Recently, nitric oxide (NO) was proposed as a possible signal transducer of circulating pyrogen-induced PGE2 synthesis in hypothalamus. In our previous study, i.c.v. administration of exogenous carbon monoxide (CO), which has very similar character with NO in biological activity, markedly increased the body temperature. So, we study the effects of hemin, which is a substrate of CO-producing enzyme (heme oxygenase, HO) and a inducer of HO, on body temperature in this study. Hemin(i.c.v.) markedly increased in body temperature and this response was blocked by ZnPP IX (inhibitor of HO), indomethacin, or cycloheximide (inhibitor of gene transcription). Hemin maximally induced HO-1 in hypothalamus at 3 hrs after administration.
These results suggest that hemin-induced pyresis is partially due to induction of HO-1 and endogenous CO is a possible signal transducer of febrile response in hypothalamus.

[PA1-38] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Effects of long-term administration of NOS inhibitor on aortic contractility

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Nitric oxide (NO) is one of the important modulators that control vascular smooth muscle tone. The chronic inhibition of NO synthase (NOS) elicits the hypertension in rats. However, the mechanism of hypertension induced by chronic inhibition of NOS is not clear. Thus, to clarify the mechanisms of occurance of hypertension, we studied the effects of adrenergic agents on aortic contractility in rats treated with NOS inhibitors for 21 days were examined.
Chronic administration of L-NAME significantly increased in the blood pressure. The pressor effect of norepinephrine and the depressor effect of prazosin were significantly increased in the L-NAME-induced hypertensive rats. Phenylephrine, a α-receptor agonist, AlF_4^-, G-protein stimulator, elicited the more potent contraction in the aorta of the rats treated with L-NAME for 21 days than in the aorta of the untreated rats. The potentiation of contractile action of phenylephrine by treatment with L-NAME for 21 days was significantly reduced in the endothelium-free aorta. However, the contractile action of phenylephrine was still more potent in the endothelium-free aorta of the rats treated with L-NAME for 21 days than in the endothelium-free aorta of the untreated rats. These results suggests that the hypertension by choronic inhibition of NOS is partially due to the changes of the intracellular signal transduction system of aortic smooth muscle.

[PA1-39] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Interrelationship between the IL-1β-induced pyresis and heme oxygenase in hypothalamus

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The thermoregulatory center located in the hypothalamus maintains physiological temperature, while fever dependens on the production of exogenous pyrogens, which induce biochemical modifications in the hypothalamus. Exogenous pyrogens can induce the release of endogenous pyrogens or cytokines (IL-1β, IL-6 and TNF-α). This in turn, leads to the production of PGE. Afterwards, PGE provokes stimulation of the neurons localized within the hypothalamus, therby triggering a reaction which culminates in the generation of fever. However, the precise mechanism by which endogenous pyrogens or cytokines increase PGE synthesis in hypothalamus is still unclear. Recently, carbon monoxide (CO) was proposed as a novel mediator of the febrile response in the central nervous system. Thus, we studied the interrelationship between heme oxygenase, a CO-producing enzyme, and IL-1β-induced febrile response. Il-1β(1.c.v. inj.) elicited the febrile response and this pyresis was significantly blocked by pretreatment with indomethacin (an inhibitor of COX), but not with ZnPP IX (an inhibitor of heme oxygenase) or ODQ (an inhibitor of soluble guanylate cyclase). IL-1β significantly induced HO-1 in hypothalamus. We couldn't find any consistent evidence that CO is a possible mediator of IL-1β-induced febrile response.

[PA1-40] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

Lipopolysaccharide-induced pyresis is not related to the heme oxygenase induction

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Peripheral administration of lipopolysaccharide (LPS) induced the release of circulating pyrogenic cytokines, and these cytokines elicit febrile response. Since the structural impermeability of cerebral capillaries and the low efficiency of any transport system for the cytokines across the capillary wall, it was proposed that circulating pyrogenic cytokines have their major effect on the rich vascular network close to the cluster of neurons in preoptic/anterior hypothalamus (ie., organum vasculosum laminae terminalis [OVLT]). However, the precise mechanism by which blood-borne cytokines increase PGE synthesis in hypothalamus is still unclear. In our previous study, i.c.v. injected carbon monoxide (CO) elicited pyresis and this response completely was blocked by indomethacin. Also, CO was proposed as a possible mediator of febrile response in hypothalamus. CO can be produced from heme oxygenase (HO)-catalyzed metabolism of heme. Thus, we studied the relationship of heme oxygenase to LPS-induced febrile response. LPS-induced pyresis was blocked by indomethacin, but not by ZnPP IX (an inhibitor of HO) or ODQ (an inhibitor of guanylate cyclase). LPS (i.p. inj.) did not induce HO-1 in hypothalamus. These results suggest that CO is not involved in LPS-induced pyresis.

[PA1-41] [10/19/2000 (Thr) 10:00 - 11:00 / [Hall B]]

The role of G protein in muscarinic receptor-mediated αAPPs release in SH-SY5Y cells

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