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Quantitative Aspects of the Fever Response Elicited by Intracerebral Injection of Endotoxin in the Guinea-Pig

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Summary

Fever developing after intracerebral injections of lipopolysaccharide (LPS) to guinea-pigs were monophasic, with only one peak of inner body temperature,slowly developing and longlasting in a dose range 20 to 200 ng of LPS. Latency time was inversely related to the dose of LPS. Indomethacin injected to the third brain ventricle did not abolish fever response.

Key words

Fever – Endotoxin – Indomethacin

Although in the recent years there have been many studies comparing the effects of bacterial pyrogens and endogenous pyrogens on fever after systemic administration, much less attention has been paid to intracerebral action of bacterial pyrogens. It was, nevertheless, clearly shown that bacterial pyrogens trigger fever response after direct application into the anterior hypothalamus or its close vicinity (Jackson 1967). It was the aim of this study to fill in the gap and perform a quantitative investigation of fever after central injections of a bacterial pyrogen in different doses.

On adult male guinea-pigs (weighing 400 – 800 g), the time courses were measured of changes of the total metabolic rate (M), oesophageal (Te) and ear (Ts) body temperatures at an ambient temperature of 26 °C after application of LPS (E. coli lipopolysaccharide, Sigma) in doses 20, 50, 100, and 200 ng to the preoptic area – anterior hypothalamus (POAH). LPS was diluted in isotonic apyrogenic NaCl and applied in a total volume of 1 μl by means of a steel cannula previously implanted into the proper place under general anaesthesia at least one week before the experiment. In control experiments, 1 μl of isotonic apyrogenic saline was injected instead of LPS. From continuous recordings, the following parameters were evaluated: latency time to the onset of fever from the moment of application of LPS (the onset was chosen as the upward change of Te by 0.2 °C above the resting level), the maximal increase of Te, time to its peak, and fever index for a 300 min interval (calculated as

$$FI_{300} = \int_0^{300} \Delta T_e(t)dt$$

where ΔT_e is the difference of Te from the resting level and t is time).

The resulting fevers which developed after intracerebral injections of LPS to awake, slightly restrained guinea-pigs were monophasic, with only one peak of deep body temperature, slowly developing and longlasting. No defervescence occurred even 5 h after injection of LPS. The latency of the onset of fever was dose dependent, diminishing with the increasing dose (Fig. 1). Other quantitative parameters of fever, i.e.

maximal increase of body core temperature, time to its peak and fever index for the 300 min interval were not dose dependent – the differences among different doses were not significant (ANOVA, significance level 0.05), although they differed significantly from the controls.

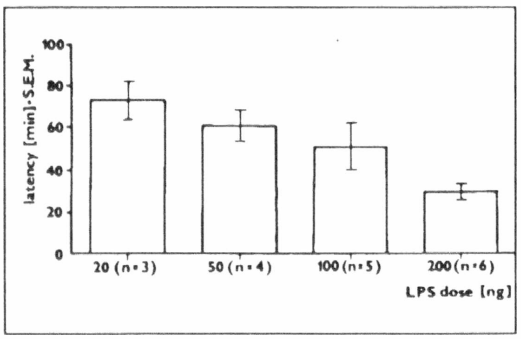

Fig.1
Latency time of the fever onset after different doses of LPS injected into POAH of guinea-pigs.Differences among effects of different doses are significant (ANOVA, & < 0.05).

Mean values for 100 ng LPS dose (± S.E.M., n = 5) were: latency time 50 ± 10 min, ΔTe_{max} 1.6 ± 0.1 °C, time to peak Te 215 ± 27 min, fever index FI_{300} 326 ± 22 °C * min.

In order to test the possible role of prostaglandins in the fever induced by intracerebral application of LPS, 100 μg of indomethacin (Sigma), a prostaglandin synthesis inhibitor (dissolved in ethanol, total volume 5 μl), was injected into the third brain ventricle 15 min before injection of LPS into POAH. It did not influence the fever response significantly (latency 60 min, ΔTe_{max} 1.0 ± 0.2 °C, time to peak 240 min, FI_{300} 203 ± 62 °C * min; n = 6).

The long latency time till the onset of fever, its monophasic course, duration and poor dependence on the dose of endotoxin after POAH administration contrast with the known characteristics of fever after intravenous administration of LPS (Blatteis 1974, Shido and Nagasaka 1986). Although animals are much more sensitive to POAH injections of LPS (effective doses were one order of magnitude lower than after intravenous administration), it does not seem probable that LPS has a direct specific effect on thermoregulatory centres. It was shown on brain slice preparations that LPS can release prostaglandins E_2 from the brain tissue (Hori *et al.* 1987). However, the presented experiments with indomethacin, as well as the long latency and duration of fever after intraPOAH application of LPS do not indicate that prostaglandins are involved in this type of fever. The mediation of the febrile effect of LPS in the brain remains speculative and some of the endogenous pyrogens known to be active in the brain tissue (e.g. macrophage inflammatory protein, Minano *et al.* 1990) could account for this.

References

BLATTEIS C.M.: Influence of body weight and temperature on the pyrogenic effect of endotoxin in guinea-pigs. *Toxicol. appl. Pharmacol.* **29:** 249–258, 1974.

HORI Y., BLATTEIS C.M., NASJLETTI A.: Production of *PGE2* by brain slices stimulated with various thermoactive agents. *Fed. Proc.* **46:** 683, 1987.

IRIKI M.: Fever and fever syndrome – current problems. *Jap. J. Physiol.* **38:** 233–250, 1988.

JACKSON D.D.: A hypothalamic region responsive to a localized injection of pyrogens. *J. Neurophysiol.* **30:** 586–602, 1967.

MINANO F.J., SANCIBRIAN M., VIZCAINO M., PAEZ X., DAVATELIS G., FAHEY T., SHERRY B., CERAMI A., MYERS R.D.: Macrophage inflammatory protein – 1: unique action on the hypothalamus to evoke fever. *Brain Res. Bull.* **24:** 849–852, 1990.

SHIDO O., NAGASAKA T.: Cardiovascular and thermal responses to intravenous endotoxin in guinea-pigs. *Jap. J. Physiol.* **36:** 543–554, 1986.

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