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An Analysis of Fever-curves due to the Intravenous vs. Intraventricular Administration of LPS Pyrogen in Rabbits

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Abstract; Fever-curves were compared on response to injection of bacterial pyrogen into conscious rabbits using different routes of administration.

Intravenous application of 0.2μg/kg LPS pyrogen to the rabbit was characterized by biphasic fever after a short delay of 10 to 30 minutes. However, monophasic fever developed when same dosage of LPS was administrated into the lateral-ventricular region. Its latency of fever onset was about 60 minutes with rectal temperature elevating by 1.5 to 2.0°C, and these febrile states continued for more than 5 hours. Based on these results, sites of pyrogen action and their underlying mechanisms were discussed in this paper.

Key words: LPS pyrogen, intravenous-, lateral ventricular-administrations, fever patterns, action sites, temperature regulation

Experiments were performed on 28 male albino rabbits weighing from 2.5kg to 3.0 kg. These animals were pyrogen negative and had no sign of infectious disease. Each animal was positioned in a stereotaxic instrument, and under aseptic and a light anesthetic condition, a hole of 0.7 mm in diameter was drilled through the skull in the midline. A guide cannula was implanted into the right lateral-ventricular region for pyrogen injection. The guide cannula was made of 23 gauge stainless steel pipe 25 mm long. The coordinates were taken from the stereotaxic atlas by Monnier and Gangloff (1961). The experiments were performed at an ambient temperature of 26°C. Rectal and ear skin temperature were measured continuously using thermister probes (Ellab Co.). To test the febrile response to pyrogen, lipopolysaccharide (LPS) from E. *coli* (B6, Difco) was dissolved in nonpyrogenic isotonic saline and injected intravenously, or into the right lateral ventricle. Precaution were taken to eliminate the probability of pyrogen contamination; injection cannula, syringes *etc*. were sterilized by an autoclave before use.

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a) Intravenous injection of LPS

0.2 μg/kg LPS pyrogen dissolved in 2 ml physiological saline was administered through the retroauricular vein of the rabbit. After the short latency of 10 to 30 minutes, bi-phasic fever curve was developed with two falling phases of ear skin temperature (Fig. 1-a). Febrile state continued for 5 hours after the injection.

b) Lateral-ventricular injection of LPS

For central administration, same dosage of LPS pyrogen was injected into the lateral ventricle followed by 10 μl saline flush through a 23 gauge injection cannula. To prevent the change of cerebral pressure, same volume of cerebrospinal liquor was drawn previously. It produced monophasic and long-lasting fever with maximal shift of rectal temperature by 1.5-2.0°C, but the latency of fever onset was approximately twice longer than that evoked by an intravenous injection (Fig. 1-b). After the start of febrile reaction, ear skin temperature began to drop, and it didn't recover to the pre-injection level even after 6 hours later.

Figure 2 demonstrated the schematic representation of fever-curves after administration of LPS pyrogen. These results are summarized in Table 1. In cases of lateral-ventricular injection, mono-phasic fever curves were elicited with only one exception. On the contrary, 20 out of 24 intravenous injection of LPS pyrogen showed bi-phasic fever at the same dosage.

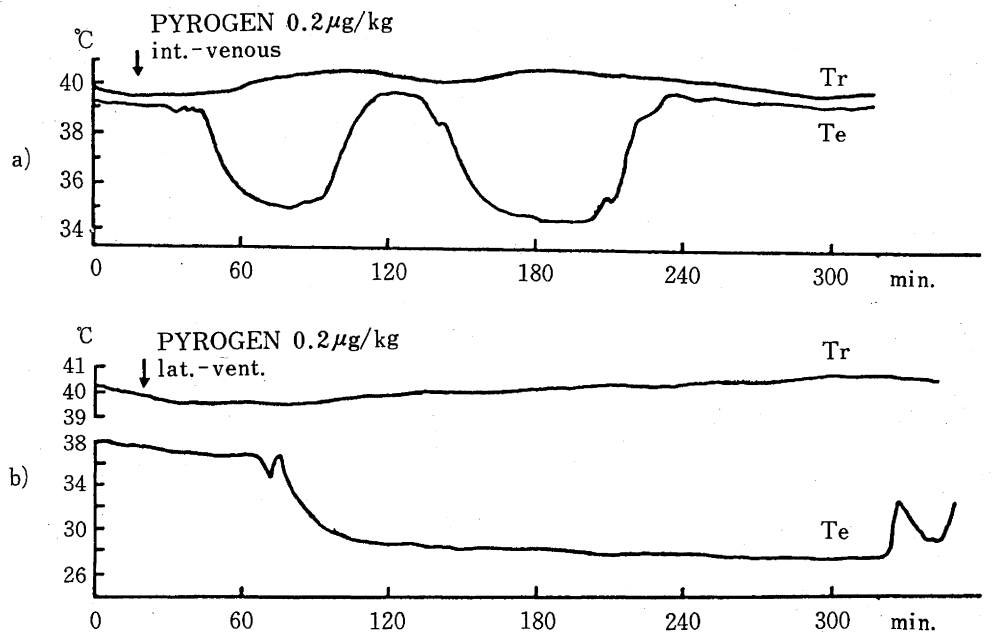

Fig. 1 Typical responses to the LPS pyrogen (0.2μg/kg wt).
a) intravenous injection (int.-venous), and b) lateral-ventricular injection (lat.-vent.).
Tr; rectal temperature, Te; ear skin temperature

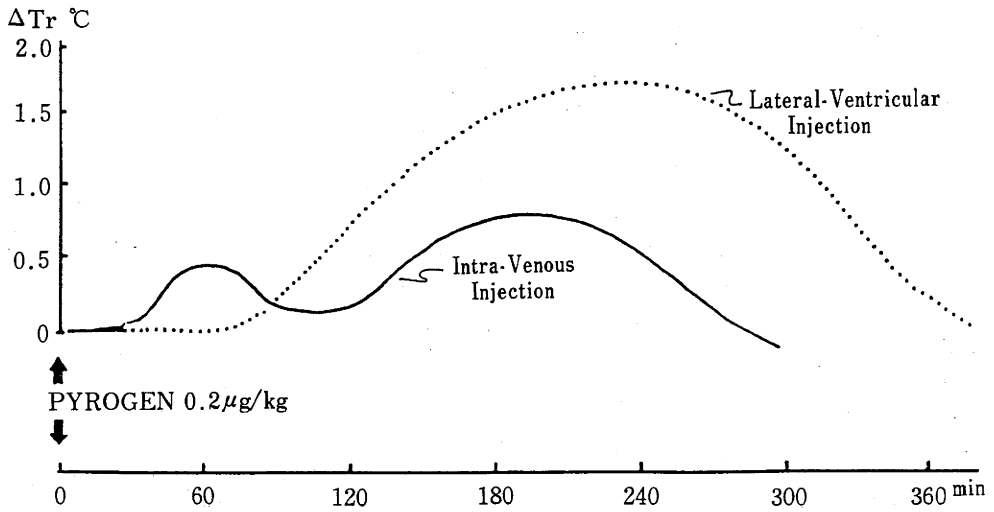

Fig. 2 Schematic representation of fever-curves after administration of LPS pyrogen. Lateral-ventricular injection (broken line), and intravenous injection (solid line) of 0.2μg/kg wt. LPS at arrows, respectively.
⊿ Tr: Shift of rectal temperature from the control state

Table 1. Types of fever-curve due to administration of pyrogen (0.2μg/kg body wt)

	Lateral-Ventricular Injection (N=18)	Intra-Venous Injection (N=24)
Mono-Phasic	17	2
Bi-Phasic	1	20
Poly-Phasic	0	2

It has recently been shown that endotoxin would cause either monophasic or bi-phasic fever depending upon the dosage. And, it was suggested that monophasic fever curve was developed after intravenous administration of excess LPS. Cerebrospinal fluid volume was about 1/25 of whole blood contents. So, in spite of the same dosage administration to body weight of LPS, it might be LPS of much concentration in the cerebrospinal space, and, in turn, it developed a larger, monophasic fever compared to intravenous injection of LPS.

The action mechanism of bacterial pyrogen, such as LPS, have not been clarified. The injection of bacterial pyrogen directly into the hypothalamus of cats (Villablaca and Myers, 1965), into the lateral ventricle in cat (Sheth and Borison, 1960) produced febrile responses. However, it was reported that bacterial pyrogen did not pass the blood brain barrier (Atkins, 1960, Ohwatari and Kosaka, 1979) and that they produce fever by provoking the release of leukocyte pyrogen (LP), which, in turn, acts on the brain to acti-

vate the central thermoregulatory mechanisms (Fujiwara *et al.*, 1984).

There is also the probability that endotoxin might act directly at peripheral thermo-effector organs. The mechanism leading to malignant hyperthermia in susceptible person following halothane anesthesia was thought to be the accumulation of free-calcium in myoplasm, and these ions directly act on skeltal muscle (Nelson and Flewellen, 1983). The exact mechanism of action of LPS remains to be investigated.

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ウサギ静脈内及び側脳室内への LPS pyrogen 投与による発熱曲線の解折

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大腸菌由来の lipopolysaccharide (LPS) を用いて，ウサギの発熱曲線の解折を行った．ウサギに体重1kg あたり0.2μg の LPS pyrogen を耳介皮膚血管から静脈内投与すると，10分から30分の短い潜時ののちに，二峰性の発熱が観察された．ところが，同濃度の pyrogen の側脳室への直接注入では，約1時間の潜時で，直腸温の上昇も1.5°C から2.0°C と，pyrogen 静注時に比較すると高い一峰性の発熱が生じた．投与部位の差異による発熱パターンの違いから，LPS pyrogen の作用部位とその働きについて考察を加えた．

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