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The Inconsistent Thermoregulatory Effector Activities Elicited by LPS-pyrogen and Lumbar Spinal Thermal Stimulation in Decerebrated Rabbits*

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Abstract: The competitive combination of stimuli, ie LPS-administration+lumbar spinal cord warming were applied to intact and midpontine-decerebrated (MPD) rabbits in oder to estimate the efficacy of LPS in extrahypothalamic thermoregulatory centers and the dominancy of these centers on varying effector mechanisms. MPD rabbits have restored shivering in response to lumbar spinal cooling at 34°C and this shivering was abolished by spinal warming at 40°C. The increase of respiratory rate was elicited by spinal warming in MPD and intact rabbits, which was diminished by LPS in intact rabbit, though little affected in MPD rabbit. LPS failed to induce shivering in both animals during spinal warming. Ear temperature was changed by spinal thermal stimulation in a discordant way, upward by cooling and downward by warming, in MPD rabbit. LPS competed the spinal-warming by resulting the rapid fall of ear temperature in intact rabbit. Nevertheless, it couldn't reduce it in MPD rabbit, rather LPS raised ear temperature of MPD rabbit with spinal warming. It is inferred that LPS would have "recovery effect" to responsiveness in the vasomotor center of MPD rabbit or the role of vasodilation resulted from spinal warming may be different from usual thermoregulatory effector mechanism facilitated by skin or core heating.

Key words: Midpontine decerebration, Extrahypothalamic thermoregulation, LPS, Ear temperature

There are many evidences that extrahypothalamic area can induce the heat production as well as heat dissipation without preoptic-anterior hypothalamic thermoregulatory center (PO/AH), and among these area, spinal cord has been paid much more attention by

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many investigators[25]. In our previous experiments, warming of lumbar spinal cord in intact rabbit induced an immediate rise in temperature of ear and pad skin with an increase of respiratory rate, accompanied by decrease of oxygen consumption and slight decrease of rectal temperature. Spinal cooling elicited these activities of effector system in opposite way as compaired with spinal warming[18]. However, dual agonistic and/or antagonostic thermal stimulation, which were applied to different thermoregulatory centers, provided uncoordinated effector activities (Jessen & Simon[15]). According to their results, heat production was increased by PO/AH cooling and spinal cooling. The effect of simultaneous cooling and/or warming in each area was summational in heat gain responses. Nevertheless, cooling of one center never inhibited the increase of respiratory rate induced by warming of another center simultaneously.

The hierarchical theory has been a central dogma to interpret the relationship of these thermoregulatory centers. But the contribution of these centers on effector mecha-

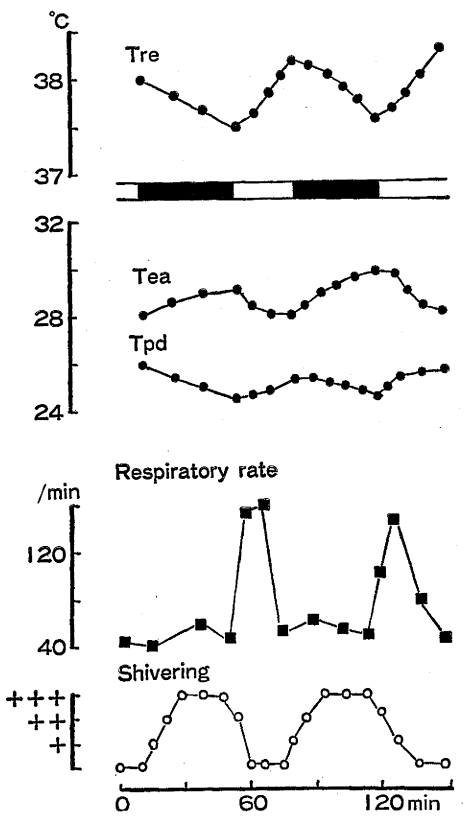

Fig. 1. Thermoregulatory responses during lumbar spinal cord warming and cooling in mid-pontine decerebrated rabbit. Note that shivering and respiratory rate show consistent responses to spinal thermal stimulation (upper graph). Ambient temperature 24°C:Tre, rectal temperature; Tea, ear temperature; Tpd, pad skin temperature. Also note the inconsistent fluctuation of ear temperature. Solid bar, spinal canal cooling; blank bar, spinal canal warming.

nisms and the neural network of varying thermocenters are still obscure. Therfore, decerebration between diencephalic area and mesen- or telencephalic area would have some advantages for revealing the interaction of the thermoregulatory centers. Our recent study showed that rabbits restored heat gain responses to skin or core thermal stimulation as the level of sectioning was lowered toward midpontine-pretrigeminal region[14], although precollicular-prepontine decerebration often failed to induce heat gain responses by thermal stimulation[16].

Several investigators have reported analogous results, however, they proposed that mesencephalic area has a tonic inhibitory action against shivering-facilitatory system of lower brain stem in species of monkey[19], cat[1)2)6)], and rat[3]. In addition, non-shivering thermogenesis was also facilitated by intercollicular-prepontine decerebration in rats[24]. So that, both shivering and non-shivering thermogenesis would have inhibitory control from mesencephalic (including upper pons) area.

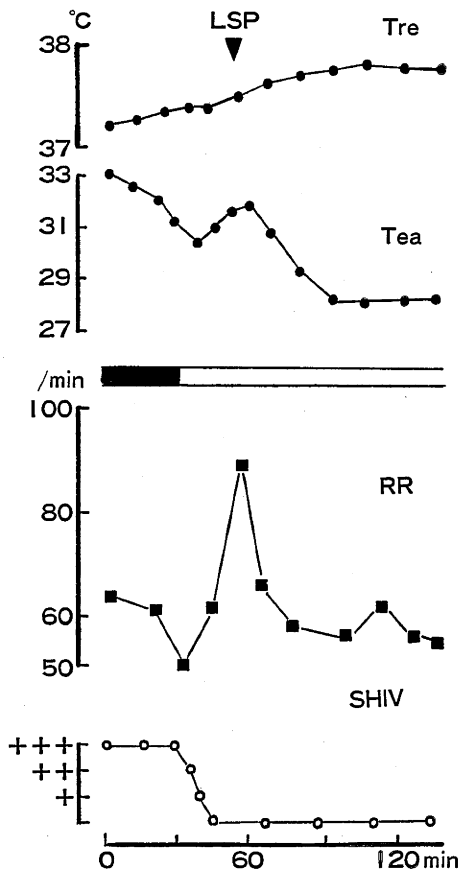

Fig. 2. Thermoregulatory responses in LPS-treated intact rabbits during spinal warming. Note that sudden decrease of respirtory rate and fall in ear temperature are elicited by LPS injection intravenously. ambient temperature, 26°C. LPS, lipopolysaccharide; RR, respiratory rate; SHIV, shivering. Other abbreviations are same as in Fig. 1.

Accordingly, present study was designed to estimate the efficay of thermal input to lumbar spinal cord in heat gain and heat-loss responses in the absence of diencephalic thermoregulatory centers. In the next place, lipopolysaccharide (LPS) was used as non-thermal cold stimulation[5)7)23)], in conjunction with spinal warming in decerebrated and intact rabbits. The relationship of lower brain stem and spinal cord, or PO/AH and spinal cord during applicating competitive stimuli are discussed.

The present experiments were performed on unanesthetized male rabbits. After decerebration at intercollicular-midpontine level, U-shaped polyethelene tubing thermode in which warm (42°C) and cool (32°C) water were perfused at the flow rate of 30 ml/min were inserted from 5th vertebral space for 5 cm upward. Continuous measurements of rectal temperature (Tre), ear temperature (Tea), pad skin temperature (Tpd), electro-myogram (EMG) of brachial triceps, respiratory rate, and oxygen consumption were made. Details of experiment have been described elsewhere[17)]. LPS of E. coli (Sigma chemical), 5μg

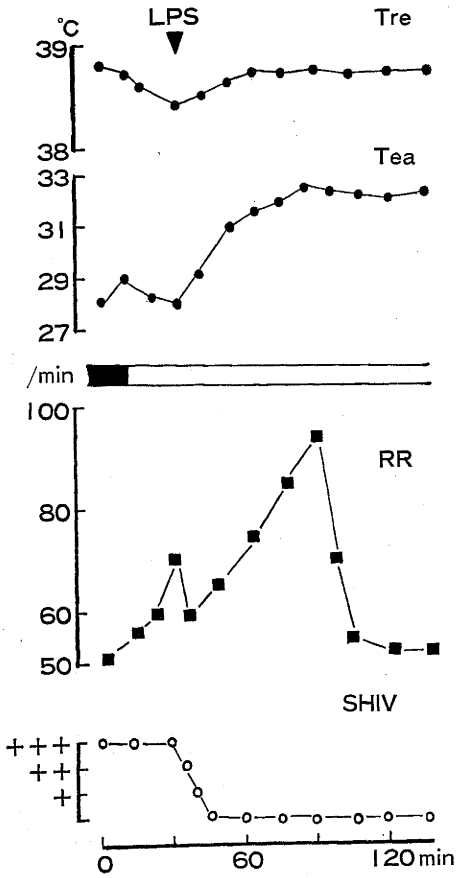

Fig. 3. Thermoregulatory responses in LPS-treated, midpontine decerebrated rabbit during spinal warming. Note that Tea gradually elevated up to 32°C, also note that increasing pattern of RR is declined after LPS injection Ambient temperature, 26°C. abbreviations are same as in Fig. 2.

in 1 ml saline, was injected into femoral vein through an indwelling catheter. It has been well known that LPS potentiates the production of prostaglandin E_2 by macrophages, and this process is intermediated by interleukin 1 (also known as "endogenous pyrogen") which is also synthetized by macrophage itself[13)20)].

In Fig. 1, decerebrated rabbit showed inconsistent effector activities during spinal thermal stimulation. Heat gain responses in respiratory rate (decrease) and shivering were not affected during spinal cooling, but the fluctuation of Tpd was attenuated and Tea rose. In spinal warming, Tea decreased rapidly; like the response to cold stimulus in intact rabbit. This observation has already been reported by Kosaka et al[17)]. In addition, change of Tre was greater than in intact rabbit, in other words, MPD rabbit might have lost fine adjustment of fore temperature although effector mechanisms were still remaining. Intact rabbit (Fig. 2) showed discordant effector activities after the administration of LPS which elicited heat gain esponses (Tea decrease and respiratory rate decrease) but failed to trigger shivering, in this case, the effect of spinal warming was dominant. This result is interesting because pyrogen is beleived to act mainly on PO/AH area and partly on brain stem[23)].

It is assumed that cold cells in lower brain stem would have outflows chiefly to vasomotor and respiratory centers, besides, cold signals induced by LPS in PO/AH area have a pivotal role of eliciting the shivering response.

If cold signals induced by LPS is equivalent to those induced by thermal stimuli (cooling) in PO/AH, our result which LPS inhibits the increase of respiratory rate elicited by spinal warming showed discrepancy compaired to the results observed by Jessen and Simon[14)]. It is inferred that a decrease of respiratory rate seen in Fig. 2 is neither the specific thermoregulatory response, nor the effect produced by endogenous pyrogen.

LPS-treated MPD rabbit showed inconsistent responses especially in ear temperature (Fig. 3). Tea gradually increased by about 5 °C one hour after LPS-injection without the rise of Tre. Respiratory rate was first depressed immedately after the injection of LPS, and then, it started to increase gradually in para lel with Tea. No shivering was observed during spinal warming. The depressive manner in respiratory rate in Fig. 3 is quite different from that in Fig. 2. In MPD rabbit, LPS failed to induce rapid inhibition as compaired with intact rabbit. It took about one hour to make the inhibition in respiratory rate. However, this period is well consistent with incubat'on time or latency of pyrogen-induced fever. It is inferred that participation of upper brain stem would be essential for inhibition of respiratory rate elicited by LPS and later inhibition in respiratory rate of MPD rabbit is presumably induced by endogenous pyrogen or prostaglandins.

It is important to recall the attitude of Tea in Fig. 1, where Tea decreased in response to spinal warming. This result is very complicated for making reasonable interpretation. It seems that LPS would have "recovery effect" on the responsiveness of vasomotor center to sptnal warming in MPD rabbit (Fig. 3). Hypothalamus has a role for reducing the systemic blood pressure[9)10)]. In this sense, decerebration itself possibly in-

duces the increase of blood flow in periphery. However, it is unlikely that spinal thermal stimulation will affect the systemic blood flow remarkably. Heat dissipation of rabbit ear is mainly achieved by increase of blood flow in arteriovenous anastomoses (AVA)[8] during spinal warming, and locally applied heat induced vasodilation in ear capillaries[12]. However, the innervation of AVA and capillaries are still unclear. The central ear artery has has adrenergic dense plexus[4], and these plexuses become lesser in branching arteries of diminishing diameter[22]. In addition, some authors proposed that small arteries in rabbit ear are histaminergic[11], and the AVA of hindpaw in dog would have dopaminergic innervation[21]. Spinal warming reduces sympathetic effector activities in intact rabbit[12], but there is no evidence of direct pathway between spinal warm sensitive tissue and medullary vasomotor center. Therefore it is concluded that warm signals from lumbar spinal cord will induce vasodilation in AVA of rabbit ear with cooperation of upper thermoregulatory centers, and LPS-induced cold signals in lower brain stem would have a compensatory effect on these systems. Another possibilility is that the physiological role of vasodilation resulted from spinal warming is different from usual thermoregulatory effector response elicited by skin by skin or core heating.

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LPS 投与と脊髄温度刺激時の橋中央部除脳ウサギにみられた効果器活動の非協調性

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LPS 及び腰部脊髄温度刺激の組合せによる競合的刺激が除脳ウサギの体温調節に対して与える影響について研究した．通常除脳ウサギでも脊髄温度単独刺激については正常ウサギと同じような反応を示すが，耳介皮膚温のみが正常と逆の反応を示した．即ち温刺激に対して低下し．冷刺激に対して上昇した．ところで正常ウサギに上記2種類の刺激を与えると，呼吸数・皮膚温に対しては LPS が優位となり抑制効果が現われるが．ふるえに対しては脊髄温刺激の方が優位である．一方，除脳ウサギでは．耳介皮膚温は LPS 投与後上昇し，呼吸数も LPS によって直ちに低下しない．ここでは，むしろ脊髄の温度刺激の方が優位となり，あたかも正常ウサギに脊髄の単独温刺激を与えたときと同じような反応を示した．このことは．LPS が「回復効果」をもたらしたものか，或は，元来脊髄温度刺激によって出現する皮膚温の上昇が，通常の皮膚温度刺激や核温度刺激によって生じる体温調節反応とは異なる作用なのか現在のところ判別できない．

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