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Perspective

Oxidative stress and pyrogenic fever pathogenesis

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ABSTRACT

The causative/regulatory connections between changes in tissue redox state and fever induction were investigated herein. Wherefore, LPS, the primary element of bacterial cell wall, in addition to inducing pro-inflammatory cytokines, activated macrophages and other leukocytes to secrete hydroxyl radical (OH), nitric oxide metabolites (NO_x^-), superoxide (O_2•) and other reactive oxygen/nitrogen species. Furthermore, inflammation response-associated hypoxia stimulated glutamate release, which caused excitotoxicity of cells by increasing extracellular Ca^{2+}. Cytokines and glutamate in turn also triggered the release of large amounts of NO_x^-, OH, O_2•, and other radicals. Those reactive nitrogen species in turn caused cellular injury via the peroxidation of membrane lipids and oxidative damage of proteins and DNA. Glutamate, NO_x^-, OH and antioxidants participated in the pathogenesis and regulation of LPS- or cytokines-induced fever. In particular, to highlight the role of glutamate, prostaglandin E_2, NO_x^- and OH generated in the hypothalamus during pyrogenic fever was attempted hereby. To find the link among the signaling with the glutamate, NO_x^- and OH•/prostaglandin E_2 in the hypothalamus during pyrogenic fever will be challenging and could now clinically suppress pyrogenic fever.

1. Lipopolysaccharide (LPS)- or cytokine-caused fever

It was described that the most frequent and serious global problem was sepsis, which was a systemic inflammatory process mostly endotoxin- or lipopolysaccharide (LPS)-caused (Bhattacharyya et al., 2004; Rangel-Frausto et al., 1995). LPS triggered the production of tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, prostaglandin E_2 (PGE_2), interferon gamma, leukemia inhibitory factor, migration inhibitory factor, platelet activating factor, products of the complement and clotting cascades, in addition to activating macrophages and other leukocytes to secrete hydroxyl radical (OH•), nitric oxide metabolites (NO_x^-), superoxide (O_2•) and other reactive oxygen/nitrogen species. Also in experimental and clinical studies, infection, trauma, or tissue anoxia stimulated macrophages and monocytes to secrete IL-1β, TNF-α, and others (Wu et al., 2008); hypoxia, glutamate release, which caused cell excitotoxicity by increasing extracellular Ca^{2+} (Cassina et al., 2002). These cytokines and glutamate in turn released large amounts of NO_x^-, OH•, O_2•, and others and resulted in cellular injury via the peroxidation of membrane lipids and oxidative damage of proteins and DNA (Cassina et al., 2002; Feihl et al., 2001).

The organum vasculosum laminae terminalis (OVLT), a circumventricular organ in the anterior wall of the third cerebral ventricle, was a site through which signaled that increased body temperatures were transferred from the blood to the hypothalamus in animals (Hashimoto et al., 1994; Stitt, 1985). According to Dinarello (2004), Gram-positive or Gram-negative organisms released endotoxins in local or systemic infection. Pyrogenic cytokines IL-1, TNF-α, IL-6 and other cytokines which were synthesized and processed accessed the circulation and were bound to the respective cytokine receptors in the OVLT. Activated Toll-like receptors (TLR) and other cytokine receptors induced cyclooxygenase-2 (COX-2), which resultantly synthesized PGE_2 on the brain side (the OVLT). Increases in hypothalamic PGE_2 released cyclic adenosine monophosphate (cAMP) and other neurotransmitters triggering thermosensitive neurons in the hypothalamus to raise the thermostatic set point. Hypothalamic signals activated peripheral efferent nerves to increase heat production and decrease heat loss. The resulting increase in blood temperature was detected by the thermoregulatory center in the hypothalamus.

This review was to update the role of glutamate, NO_x^- and OH• and antioxidants in the pathogenesis of LPS- or cytokines-induced fever, particularly to focus the role of glutamate, PGE_2, NO_x^- and OH• in the hypothalamus generated during pyrogenic fever.

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2. Glutamate in pyrogenic fever

The amino acid glutamate, the major excitatory neurotransmitter in the central nervous system, was important in learning, memory, development, and other forms of synaptic plasticity (Said et al., 1996). The ionotropic N-methyl-D-aspartate (NMDA) receptor was the focus of much attention because of its implication in heat injury, strokes, epileptic seizure, Alzheimer disease, Huntington disease, Parkinson disease, amyotrophic lateral sclerosis and dementia. The aspirin neuroprotective effect by inhibiting glutamate release after permanent focal cerebral ischemia in rats was also shown (De Cristobal et al., 2002).

Cyclooxygenase-2 was implicated in excitotoxic cell death and, currently, this inducible enzyme is regarded as a potential therapeutic target for neuroprotection (Pepicelli et al., 2005). In vivo activation of NMDA receptors in the rat hippocampus immediately and transiently increased the PGE_2 basal levels (Pepicelli et al., 2002). The increased PGE_2 caused by NMDA receptor activation was prevented to a similar extent by the specific NMDA antagonist MK801 and by selective/non-selective COX-2 inhibitors, indicating that the NMDA-evoked PGE_2 synthesis largely depended on COX-2 activity. LPS activated the hypothalamic–pituitary–adreno-cortical axis and brain stem nuclei (Ericsson et al., 1994) and affected norepinephrine, dopamine, serotonin (Molina-Holgado and Gauza 1996) and glutamate activities (Lin et al., 1999). It was likely that LPS might cause fever via stimulating NMDA-dependent hydroxyl radical–PGE_2 pathway in the hypothalamus.

Intravenous staphylococcal enterotoxin A produced fever accompanied by increasingly released glutamate in the rabbit hypothalamus (Huang et al., 2001). Applied NMDA receptor antagonists significantly attenuated the staphylococcal enterotoxin A and induced augmenting glutamate release in the hypothalamus and fever which could be induced by directly administrated glutamate into the hypothalamus and greatly reduced by pretreatment with intrahypothalamic NMDA receptor antagonist (Huang et al., 2001). Both the fever and augmented glutamate release in the hypothalamus after intravenous staphylococcal enterotoxin A were significantly reduced by pretreatment with intravenous cyclooxygenase inhibitors such as aspirin, sodium salicylate, acetaminophen, or diclofenac (Huang et al., 2004a,b). Intrahypothalamically administrated aspirin or sodium salicylate significantly suppressed the glutamate-induced fever (Huang et al., 2004a,b). Several in vivo findings also demonstrated that glutamatergic neuron discharge promoted the extracellular release of hydroxyl radicals (Yang et al., 1995). Intravenous LPS elicited a biphasic febrile response, with the core temperature maxima at 80 and 200 min post-injection. Each core temperature rise was accompanied by a distinct wave of cellular concentrations of 2,3-DHBA (an index of the level of hydroxyl radicals) in the hypothalamus (Huang et al., 2006). The rise (following systemic injection of LPS) in both the core temperature (early or late fever) and hypothalamic 2,3-DHBA could be induced by directly injected glutamate into the cerebroventricular fluid system, and was significantly antagonized by pretherapeutic injection of α-lipoic acid, N-acetyl-L-cysteine, MK-801, or LY235959 1 h before LPS injection. The LPS-increased PGE_2 in the hypothalamus could be suppressed by free radical scavengers like α-lipoic acid or N-acetyl-L-cysteine. In these findings, an NMDA receptor-dependent hydroxyl radical–PGE_2 pathway in the hypothalamus of rabbit brain could mediate the LPS-induced fever (Huang et al., 2006). Indeed, lipopolysaccharide- and glutamate-elevated hypothalamic hydroxyl radical and fever could be NMDA receptor antagonism-suppressed (Kao et al., 2007).

3. Nitric oxide in pyrogenic fever

Nitric oxide metabolites (NO_x^-) were generated by three isoforms of nitric oxide synthase (NOS), two of which were expressed constitutively (in endothelium: endothelial NOS, eNOS; brain: neuronal NOS, nNOS), while the other one was endotoxin- or cytokine-induced (inducible NOS, iNOS) (Thiemermann, 1997). Expressed iNOS in many organs or tissues in Gram-negative or Gram-positive bacteria-caused septic shock resulted in an enhanced NO_x^- that contributed to hypotension, vascular hyperactivity to vasoconstrictors, organ injury and dysfunction as well as host defense. The inhibited iNOS (e.g., with dexamethasone) or iNOS (e.g., with selective inhibitors of iNOS activity) exerted beneficial effects in septic shock animal models; the inhibited eNOS, excessive vasoconstriction (adverse effects) plausibly.

LPS stimulated the acute early release of pro-inflammatory cytokines like TNF-α, IL-1β, and others from macrophages and leukocytes (Bhattacharyya et al., 2004); these pro-inflammatory cytokines, the expression and activation of iNOS; NO_x^-, the biosynthesis of PGE_2, so it could be propyretic in the hypothalamic mediation of the pyrogenic fever (Gerstberger, 1999; Schmidt et al., 1998; Simon, 1998; Steiner and Branco, 2003; Steiner and Branco, 2001). NO_x^--dependent cyclic GMP production in glial cells could be LPS- or cytokines-modulated (Simmons and Murphy, 1993). Blockaded NO_x^- production promoted down-regulation of COX-2 activity and decreased PGE_2 production (Perkins and Kniss, 1999). According to Dinarello (2004), fever induced by IL-1, TNF-α, IL-6 or Toll-like receptor ligands required COX-2, production of PGE_2 and activation of hypothalamic PGE_2 receptors. It was likely that iNOS-dependent NO_x^- might be in the hypothalamic mediation of PGE_2-related fever.

In the light of the above, Lin and Lin (1996b) were to ascertain whether iNOS-dependent NO_x^- in the hypothalamus (or OVLT) participated in hypothalamic mediation of pyrogenic fever. In conscious rabbits, microinjected LPS, several chemically different NO_x^- donors, the cyclic GMP analog-8-Br-cyclic GMP, or PGE_2 into the OVLT caused a dose-related fever, which appeared secondary to decreased heat loss (due to peripheral vasoconstriction) and/or increased heat production (thermogenesis) secondary to shivering (Lin and Lin, 1996b). Dexamethasone [a potent inhibitor of the iNOS transcription as well as the protein synthesis, anisomycin, iNOS inhibitors like aminoguanidine, L-NMMA, and L-NIO, but not eNOS inhibitor like L-NAME (Rees et al., 1990; Szabó et al., 1994; Wu et al., 1995)] significantly attenuated the LPS-induced fever in rabbits. (Lin and Lin, 1996a,b). Pretreatment with an iNOS inhibitor like dexamethasone not only reduced the fever but also attenuated the iNOS-dependent NO_x^- production in the OVLT following an intra-OVLT dose of LPS (Lin et al., 1997), which indicated that iNOS-dependent NO_x^- in the hypothalamus played a pyretic role in rabbits. Inhibited iNOS was also to suppress LPS-, psychological stress- (Soszynski, 2001), and IL-1β-induced fever (Roth et al., 1998) in rats. In these observations, LPS or pro-inflammatory cytokines might act on the COX-2-dependent PGE_2–cAMP pathway in the OVLT (Dinarello, 2004) to induce fever via stimulating iNOS-dependent NO_x^- production in situ.

On the contrary, other lines of evidence indicated that NO_x^- inhibited LPS-induced COX-2 activity (Clancy et al., 2000; D'Acquisto et al., 2001; Deeb et al., 2006; Tanaka et al., 2001) and therefore was antipyretic (Feleder et al., 2007; Mathai et al., 2004). It should be mentioned that eNOS-dependent NO_x^- mediated peripheral vasodilation (Corbett et al., 1992). Activated eNOS-dependent NO_x^- caused by some certain circumstances might increase heat loss and decrease body core temperature.

Other lines of evidence proposed a role of NO_x^- as a signal transducing agent in febrile response by early decreased NO_x^- production in the plasma following LPS, as evaluated by falling plasma nitrate levels, which inversely correlated with the fever height (Riedel, 1997). Likewise, conversely, in methylene blue-pretreated rabbits, plying LPS was followed by rising plasma nitrate levels and abolishing oxygen radical formation, and fever was completely prevented despite elevated PGE_2 and TNF-α in the plasma (Weihrauch and Riedel, 1997). As mentioned, eNOS-dependent NO_x^- mediated vasodilation (Corbett et al., 1992). Administrated LPS might reduce heat loss (vasoconstriction) via getting decreased and releasing eNOS-dependent NO in the plasma.