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PAF is a potent pyrogen and cryogen in rodents, but it does not mediate thermoregulatory responses to bacterial endotoxin

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Concordance between lipopolysaccharide and platelet activating factor - mediated events have suggested that the latter likely mediates all effects induced by the former. In this issue of *Temperature*, Steiner and Romanovsky challenge this notion, showing that while platelet activating factor is a potent pyrogenic mediator, the thermoregulatory responses to lipopolysaccharide are instead induced by prostaglandins.

The widely used bacterial endotoxin lipopolysaccharide (LPS) is believed to exert part of its proinflammatory actions through endogenously generated platelet activating factor (PAF) – an ether phospholipid known for its proinflammatory capabilities (reviewed in ref. 1). This assumption is based on the observation that some responses such as arterial hypotension, pulmonary oedema, reduced cardiac output, hypoxia and mortality induced by LPS are antagonized by PAF receptor (PAF-R) antagonists (reviewed in ref. 2). Moreover, genetically engineered mice that overexpress PAF-R are hyperresponsive to LPS and deletion of PAR-R diminishes LPS-initiated events.[1] These observations have led to a general notion that **"PAF is a common mediator of LPS effects"**.[2,3] However, in the current issue of "Temperature" Steiner and Romanovsky.[4] challenge this notion and conclude that while PAF is a highly potent endogenous pyrogenic and cryogenic mediator, the thermoregulatory responses initiated by LPS are not mediated by PAF, but rather by prostaglandins.[4,5,63] Thermoregulatory mechanisms initiated by bacterial endotoxin LPS have been studied in the past.[7] In a warm environment, rats and mice respond to LPS with fever, which consists of more than one phase. Total vagotomy attenuates the fever response to very low doses of LPS, but is ineffective against higher doses. On the other hand, in a cold environment animals respond to high doses of LPS with hypothermia, and vagotomy exaggerates this response. Further, the authors suggest that changes in the expression of a large number of proteins involved in the synthesis, transport, and degradation of prostaglandin (PG) E_2 are the underlying causes of fever and hypothermia, and that neither response depends on the production of PAF. Studies involving specific cyclooxygenase (COX)-1 and COX-2 inhibitors.[6] that abrogated LPS-induced febrile response also support this conclusion.

Although multiple similarities exist between PAF and LPS-induced proinflammatory events, the following observations led the authors to question PAF as the underlying mediator of all LPS–induced effects: a) first, there are only a limited number of previous studies implicating the PAF-R in the LPS-induced thermoregulatory responses; b) there is a potential lack of specificity of PAF-R antagonists that may have off target actions; and c) previous studies did not control for fluctuations in ambient temperature that may have affected prior results.

Although, the authors report the involvement of prostaglandins such as PGE_2 in LPS-induced febrile response, PAF is at least 170 times more potent in inducing fever than PGE_2 – the most widely studied prostaglandin pyrogen. Another noteworthy outcome of this study is the lack of evidence for a role of prostaglandins in PAF-induced febrile response, yet PAF is capable of inducing COX-2 in isolated cells of diverse origin that yields PGE_2. In conclusion, the authors of this study.[4] show that the PAF-R does not appear to have a role in LPS-induced fever, yet for other responses PAF remains a potent pyrogen and cryogen.

Comment on: Steiner AA, Romanovsky AA. Platelet-activating factor is a potent pyrogen and cryogen, but it does not mediate lipopolysaccharide fever or hypothermia. Temperature 2015; 2; http://dx.doi.org/10.1080/23328940.2015.1030540

Keywords: cyclooxygenase, endotoxin, febrile response, PAF, LPS, PGE_2, PAF-R, thermoregulation, vagotomy

Abbreviations: COX, cyclooxygenase; LPS, lipopolysaccharide; PAF, platelet activating factor; PAF-R, platelet activating factor-receptor; PGE_2, prostaglandin E_2

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No potential conflicts of interest were disclosed.

References

1. Prescott SM, et al. Annu Rev Biochem 2000; 69:419-45; PMID:10966465; http://dx.doi.org/10.1146/annurev.biochem.69.1.419
2. Ivanov AI, et al. J Physiol 2003; 553:221-8; PMID: 14565987; http://dx.doi.org/10.1113/jphysiol.2003.055616

3. Watanabe J, et al. J Biol Chem 2003; 278:33161-8; PMID:12810708; http://dx.doi.org/10.1074/jbc.M305321200
4. Steiner AA, et al. Temperature 2015; 2:535-42; http://dx.doi.org/10.1080/23328940.2015.1030540
5. Steiner AA, et al. PLOS Biol 2006; 4:e284; PMID:16933973; http://dx.doi.org/10.1371/journal.pbio.0040284
6. Ivanov AI, et al. Front Biosci 2004; 9:1977-93; PMID:14977603; http://dx.doi.org/10.2741/1383
7. Romanovsky AA, et al. Front Biosci 2005; 10:2193-216; PMID:15970487; http://dx.doi.org/10.2741/1690