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The ins and outs of prostaglandin E2 in fever

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Sustained fever derives from prostaglandin E_2 (PGE_2) synthesized by brain capillary endothelial cells.[1] The "net fever signal" results from a) PGE_2 synthesis, translocation, and receptor activation,[1] and b) PGE_2 metabolic inactivation. Our understanding of the PGE_2 synthesis and signaling is robust. Much less clear is how systemic PGE_2 is translocated across the brain capillary endothelium into the brain parenchyma, how PGE_2 synthesized in the endothelium is vectorially directed toward the parenchyma, or how the parenchyma is cleared of PGE_2 when it is time to terminate the fever.

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Abbreviations: CSF, cerebrospinal fluid; HPGD, hydroxyprostaglandin dehydrogenase; LPS, lipopolysaccharide; MRP4, multidrug resistance transporter 4; PGE_2, prostaglandin E2; PGs, prostaglandins; PGT, prostaglandin transporter; SLCO2A1, gene name for PGT.

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Hosotani et al[2] have contributed to solving these puzzles by localizing the prostaglandin transporter PGT (SLCO2A1) in the brain of rodents before and after administration of lipopolysaccharide (LPS). PGT was the first transporter discovered for which PGs are the substrate; it rapidly transports PGE_2 with an affinity constant of ~50–100 nM, depending on the species.[3] PGT is a lactate/prostaglandin exchanger that is poised energetically solely for PG uptake across the plasma membrane.

In contrast, newly-synthesized PGE_2 effluxes from cells via multidrug resistance transporter 4 (MRP4).[4] Although MRP4 is expressed at the endothelial luminal membrane, indicating that PGE_2 would be released by these cells into the bloodstream, PGT is expressed at the same membrane and, by a process of "sided reuptake" can salvage luminal PGE_2 and direct it back toward the abluminal side [5] (**Fig. 1**, green arrows #1–2). In this regard, Hosotani et al[2] report endothelial expression of PGT in blood vessels of the subarachnoid space and choroid plexus after LPS injection. These data might indicate a role for PGT in directing PGE_2 to the parenchyma.

Alternatively, or in addition, PGT in the brain might mediate PG clearance. Normally, PGs taken up by PGT are delivered to cytoplasmic oxidative enzymes, especially 15-hydroxy prostaglandin dehydrogenase (HPGD), for metabolic inactivation. Both PGT and HPGD in the same cell are required to generate the inactive metabolite 15-keto-PGE_2.[6] Other transporters that mediate PG uptake have also identified, and some of these are also expressed in the brain (summarized in ref. 4). Assuming that all of these "non-MRP4" PG transporters function, like PGT, in the direction of PGE_2 uptake from blood to cytoplasm, then cell types expressing these PG transporters might be expected to also express HPGD. Surprisingly, HPGD is not expressed in rat brain except to a small extent in the choroid plexus; in particular, there is no discernable HPGD expression in the parenchyma or the vasculature.[7] Therefore, termination of PGE_2 signaling in fever likely does not occur within the brain parenchyma, but rather outside it. Since the brain parenchyma is surrounded by cells with plasma membranes, and since PGE_2 does not readily penetrate plasma membranes by simple diffusion,[3] PGE_2 must be pumped out of the brain parenchyma. How and where does this transport occur?

Figure 1 shows the putative role of PGE_2 transporters in the removal and inactivation of PGE_2 from the parenchyma (red arrows #3–6). PGE_2 could be transported in a single step from the parenchyma across the blood brain barrier into the circulation (red arrow #3), after which it would be taken up by distant cells and enzymatically inactivated. Alternatively (or in addition), PGE_2 could be cleared in 2 steps. The first would be transport (or even simple diffusion) from the parenchyma across the ependymal layer or pia into the CSF (red arrow #4). The second step would transport PGE_2 into the blood across the CSF blood barrier at the choroid plexus (arrow #5) and/or the arachnoid villus (arrow #6). The novel localization of PGT in the arachnoid membrane, described by Hosotani et al,[2] is consistent with a role for PGT in PGE_2 clearance.

Although PGT and other PG transporters have been localized to varying degrees in the brain, we have little information about the dynamic regulation of these transporters in the various phases of fever. Although Ivanov et al showed that PGT mRNA expression in

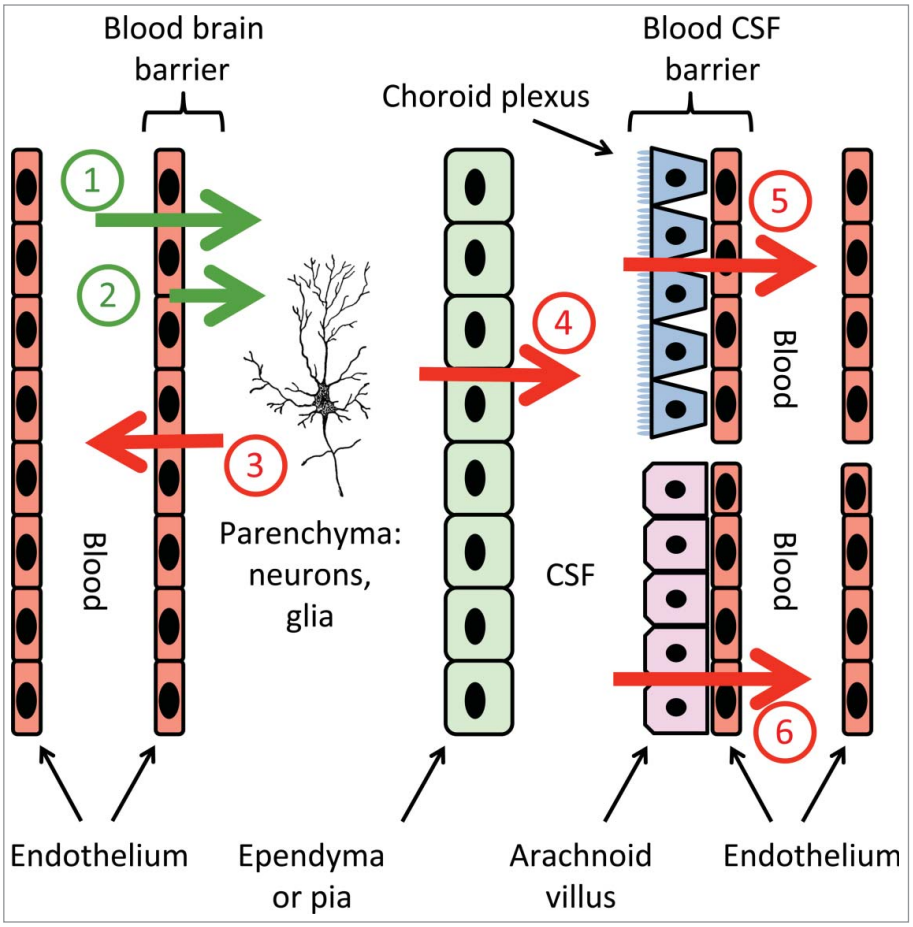

Figure 1. Transport pathways that might be involved when PGE_2 signals fever in the brain. The green arrows show translocation of systemic PGE_2 across the brain capillary endothelium, or the sided release of endothelium-derived PGE_2, into the brain parenchyma. The red arrows show termination of PGE_2 signaling via removal of PGE_2. Numbers on arrows are discussed in the text.

the late phase of LPS-induced fever declined in liver and lung, there was no change in PGT mRNA expression in the hypothalamus in the early, mid, or late phase.[8] The report by Hosotani et al expands on these dynamic studies with new information on the change of PGT expression in the brain in an LPS model.[2] They have correlated the CSF PGE_2 concentration after LPS administration with the expression levels of PGT mRNA in subarachnoid vessels and arachnoid membranes. Temporally, these correlations suggest a role for PGT in the clearance of PGE_2 (arrows #3 and #6 in **Fig. 1**).

Much work remains, but another important piece of the puzzle has been put into place.

Disclosure of Potential Conflict of Interest

No potential conflicts of interest were disclosed.

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