Mediators of infection-induced fever and associated mood alterations

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Systemic inflammation induces several symptoms mediated by the brain. These include fever and mood alterations. Prostaglandins are key mediators of many inflammatory symptoms. Prostaglandin E2 is synthesized by the brain endothelium in response to circulating cytokines including interleukin-1, and induces fever by binding to EP3 receptors in the preoptic hypothalamus. However, other brain-mediated symptoms such as loss of appetite and discomfort/aversion are not dependent on prostaglandin E2 synthesis in the brain endothelium or EP3 receptors, despite being prostaglandin-dependent. Inflammation-induced discomfort, as assayed with conditioned place aversion, is instead elicited by a mechanism dependent on cyclooxygenase-1 in microglia, EP1 receptors on striatal neurons and reduced dopaminergic signaling. In conclusion, several prostaglandin-dependent pathways work in parallel to orchestrate the systemic response to inflammation.

Central mechanism of neurogenic fever

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Neurogenic fever (NF) often occurs after acute brain injury, such as brain hemorrhage. NF is deleterious to the injured brain and needs to be suppressed. However, its precise control is hampered by the lack of information about the molecular mechanism of NF. In this study, we aimed to examine whether NF involves the central production of prostaglandin E_2 (PGE_2), as in the case of fever under infectious/inflammatory conditions. We used a murine model of NF, in which hemorrhage was induced by microinjection of collagenase into the preoptic area, the thermoregulatory center. Diclofenac and ketoprofen, non-selective cyclooxygenase (COX) inhibitors, significantly, but partially, suppressed NF suggesting a partial involvement of PG system. SC560, a COX-1 specific inhibitor, was effective in reducing NF and PGE_2 levels in hemorrhaged region. To further confirm the involvement of PGE_2 in NF, we examined NF and levels of PGE_2 in the hemorrhaged region both in wild mice and mice deficient for microsomal PGE synthase1 (mPGES1), an enzyme crucial to the synthesis of PGE_2. In mPGES1-deficient mice, PGE_2 production was almost completely suppressed whereas the suppression of NF was partial. There was a linear relationship between the size of hemorrhage and the degree of NF both in wild mice and mPGES1-deficient mice. However, the regression line for mPGES1-deficient mice was shifted downwards compared to that for wild mice. These results indicate that NF in the current murine model is brought about by both PGE_2-dependent and PGE_2-independet mechanisms.

Difference in central circuit mechanisms of infection-induced and psychogenic fever

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Fever is widely recognized as an important pathological sign. Although fever is one of the most fundamental physiological responses to systemic infections, similar elevation of body temperature is caused by psychological stress or by traumatic injuries in the brain. These three types of “fever” are called infection-induced fever, psychogenic fever, and neurogenic fever, respectively. Recent studies have revealed differences in the brain mechanisms among these three types of fever. In this talk, I will focus on the overlaps and differences between the central mechanisms for infection-induced fever and psychogenic fever (psychological stress-induced hyperthermia). These two types of fever involve a similar repertoire of sympathetic responses, such as brown adipose tissue thermogenesis, cutaneous vasoconstriction, and tachycardia, which all contribute to the elevation of body temperature. These sympathetic responses elicited by either infection or psychological stress are commonly driven by sympathetic premotor neurons in the rostral medullary raphe (rMR) to develop infection-induced fever and psychogenic fever. However, antipyretics (cyclooxygenase inhibitors), which block infection-induced fever, have no effect on psychogenic fever. In addition, prostaglandin (PG) EP3 receptor-deficient mice fail to develop fever in response to immune challenges, but do display psychogenic fever. Therefore, infection-induced fever is triggered by the PGE_2–EP3 mechanism, whereas psychogenic fever is not. Recently, we have found that psychogenic fever is triggered by stress-driven neural signaling through a prefrontal cortex–dorsomedial hypothalamus–rMR pathway, which requires no PGE_2 production. Understanding the differences in the mechanisms among these types of fever would be important in diagnosing a variety of diseases.