

FEVER AND HPA-AXIS ACTIVATION IN RESPONSE TO LOCALIZED PERIPHERAL INFLAMMATORY STIMULATION

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Fever and the activation of the hypothalamic-pituitary-adrenal (HPA) axis are characteristic brain controlled components of the acute-phase response which result, in most cases, from peripheral signals entering the central nervous system. In experimental animals the acute-phase response can be induced by systemic administration of bacterial lipopolysaccharide (LPS) which, in turn, causes a circulating cascade of proinflammatory cytokines. These cytokines, namely interleukin- (IL-) 1, IL-6 and tumor necrosis factor (TNF), are traditionally regarded as humoral factors which are involved in the induction or maintenance of brain controlled sickness signs including fever and HPA-axis activation. More recently a role of afferent fibers of the vagus nerve in transmission of inflammatory immune signals from the body periphery to the brain has been proposed since subdiaphragmatic vagotomy attenuates fever, sickness behavior and HPA-axis activation under certain experimental conditions. In this study we investigated whether also afferents from cutaneous nerves can act as a neural route for immune-to-brain communication. Male guinea pigs (*Cavia aperea porcellus*) were anesthetized with 100 mg/kg ketamine and 4 mg/kg xylazine and the following components were chronically implanted: biotelemetry transmitters for measurement of body temperature into the abdominal cavity; catheters for blood sampling into the carotid artery; cylindrical teflon chambers, open at both sides and equipped with a catheter for drug injection or collection of lavage fluid, into a subcutaneous cavity. Both, injection of a high (100 µg/kg) or a low (10 µg/kg) dose of LPS into the subcutaneously implanted chambers induced fever. An activation of the HPA-axis as indicated by increased levels of circulating cortisol only occurred in response to the high LPS-dose. The febrile response to the low, but not to the high dose of LPS, was significantly attenuated but not completely abolished by administration of 10 mg/kg of the local anesthetic ropivacaine into the inflamed subcutaneous tissue area, a procedure which blocked the transmission of afferent neural signals from this area for 6-8 hours. HPA-axis activity was not altered by treatment with the local anesthetic. This finding indicated a participation of humoral and, in response to the low LPS dose, also neuronal signals in the induction of the brain controlled fever response. In order to investigate which humoral signals may derive from the local site of inflammation we measured circulating levels of LPS (limulus amoebocyte lysate endotoxin assay) and proinflammatory cytokines (specific bioassays for TNF, IL-1 and IL-6) at distinct time intervals prior and after injection of LPS into the subcutaneous chamber. With the exception of one animal injected with the high LPS-dose, LPS was not detectable in plasma after its administration into the chamber. In response to LPS, proinflammatory cytokines were produced in high concentrations within the inflamed subcutaneous tissue area and could be measured in lavage fluid collected through the catheter of the implanted chamber. From these cytokines only IL-6 spilled over from the subcutaneous chamber area into the circulation in considerable amounts. In response to the low dose of LPS, IL-6 was the only cytokine which could be detected in plasma at all. In conclusion, IL-6 is a likely candidate to act as a humoral signal which participates in fever induction in this experimental model of a localized subcutaneous inflammation.

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