IMMUNE-TO-BRAIN SIGNALING AND CENTRAL PROSTAGLANDIN E2 SYNTHESIS IN FASTED RATS WITH ALTERED LIPOPOLYSACCHARIDE-INDUCED FEVER, -THE ROLE OF LEPTIN

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Background- Acute starvation attenuates the fever response to pathogens in several mammalian species. The underlying mechanisms responsible for this effect are not fully understood, but may involve a compromised immune and/or thermoregulatory function, both of which are prerequisites for fever generation. Leptin, an adipocyte-derived hormone, has emerged as a key regulator of starvation-related alteration of both immunity and thermoregulation. Procedure- Herein, we addressed two questions 1) whether the impaired immune-to-brain signaling or the altered thermoregulation contributes to the reported attenuation of the fever response in fasted rats during lipopolysaccharide (LPS)-induced inflammation and 2) if leptin contributes to this phenomenon. Results- Animals fasted for 48 h exhibited a significant and progressive hypothermia prior to drug treatment, which was associated with a decline in plasma leptin levels. An intraperitoneal injection of LPS resulted in a significantly attenuated fever in the fasted animals when compared to the fed counterparts. This attenuation was accompanied by the diminution in plasma levels of some [leptin, tumor necrosis factor and interleukin (IL)-1 receptor antagonist] but not all (IL-1β and IL-6) of the cytokines elevated in association with the fever response. Nevertheless, fasting had no effect on the pyrogenic inflammatory responses at the level of the brain as assessed by mRNA expressions of inhibitory factor κB, a suppressor of cytokine signaling-3, IL-1β, cyclooxygenase-2, and microsomal prostaglandin E (PGE) synthase-1 in the hypothalamus, or on PGE2 elevations in the cerebrospinal fluid. In contrast, fasting significantly attenuated the fever response to central PGE2 injection in a manner that paralleled the pre-fever hypothermia induced by fasting alone, thus implicating altered thermoregulation in the fever attenuation. Repletion of leptin in fasted animals significantly recovered the hypothermia and attenuation of PGE2-induced fever. Conclusions- These results show that neither fasting nor reduced leptin levels alters the febrigenic signaling from the periphery to the brain important for central PGE2 synthesis, but does appear to affect thermoregulatory mechanisms downstream of and/or independent of central PGE2 action.