LEPTIN AND IMMUNE-TO-BRAIN COMMUNICATION DURING SYSTEMIC INFLAMMATION

Rummel C(1,2), Inoue W(2), Sachot C(2), Poole S(3), Hübschle T(1) and Luheshi GN(2)

1) Department of Veterinary Physiology, Justus-Liebig-University, Giessen, Germany 2) Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada 3) Department of Endocrinology, National Institute for Biological Standards and Control, Potters Bar, United Kingdom

Background- Leptin, an adipose-derived hormone known to control appetite and energy balance, has emerged as an inflammatory mediator interacting with cytokines. Previously, we have shown that leptin like interleukin-6 plays an important role in immune-to-brain signaling during systemic inflammation. In this study, using signal transducer and activator of transcription (STAT)3-immunohistochemistry, we revealed a direct action of endogenous leptin on specific brain areas and cell types, all situated at the interface between the periphery and the brain and on chemokine expression in the hypothalamus, suggesting a contribution of leptin to cell trafficking. Here we aimed to investigate the role of leptin in the invasion of neutrophil granulocytes, which constitute a first line of defense against invading pathogens, during LPS-induced systemic inflammation.

Procedure- Leptin (obob), leptin receptor (dbdb) deficient mice, wild type (WT) controls and WT animals starved for 48h were injected systemically with LPS or saline and brains analyzed 24h later using immunohistochemical detection of a neutrophil specific marker protein and the intercellular adhesion molecule 1 (ICAM1) and performing real-time PCR on hypothalamic tissue. Results- Neutrophil invasion occurred in the same specific distribution pattern as previously seen for leptin induced STAT3-activation of brain cells along blood vessels situated around the lateral ventricles, the ventrobasal hypothalamus, the brainstem and meninges throughout the brain of WT animals, which was totally absent in obob and dbdb mice or significantly attenuated by starvation or after acute neutralization of endogenous circulating leptin in these animals. This response was accompanied by hypothalamic changes in levels of IL-1β and mediators implicated in cell invasion including keratinocyte-derived chemokine, macrophage inflammatory protein 2, monocyte chemotactic protein-1, ICAM1 and the tissue inhibitor of metalloproteinase 1. Some of these changes were reversed with leptin replacement in obob or starved WT animals. Conclusions- These results demonstrate unequivocally that leptin is involved in regulating neutrophil trafficking into the brain, an important blood borne signaling pathway from the periphery to the brain, most likely via modulation of IL-1β, chemokine and ICAM1 expression in the hypothalamus with possible implications for individuals with abnormal circulating leptin levels, as observed during obesity or anorexia.