SPATIOTEMPORAL ACTIVATION OF THE TRANSCRIPTION FACTOR NF-IL6 DURING THE TIME COURSE OF LPS-INDUCED FEVER IN THE RAT BRAIN

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Background- Intraperitoneal injection of lipopolysaccharide (LPS), a compound of gram negative bacterial cell walls, is known to induce brain-controlled sickness type responses such as fever. In the course of LPS-induced systemic inflammation early genomic activation of brain-cells occurs in a largely characterized distribution pattern, which can be monitored by immunohistochemical detection of the nuclear factor \( \kappa \) B (NF\( \kappa \)B) and the signal transducer and activator of transcription 3 (STAT3) and is linked to the initiation of the febrile response. Here we aimed to investigate if NF-IL6, a member of the C/CAAT enhancer binding protein family of transcription factors might be another possible participant in mediating LPS-induced activation of brain cells during fever. Procedure- Rats were injected systemically with LPS (100 µg/kg) or saline and brains were analyzed by immunohistochemistry 4, 6, 8 and 10 hours later. To determine the phenotype of reactive cells, NF-IL6-immunohistochemistry was combined with the detection of specific cell marker proteins. In addition, RT-PCR for NF-IL6-responsive inflammatory target genes was performed. Results- Moderate to strong LPS-induced nuclear NF-IL6-immunoreactivity (IR) occurred in a time dependent manner within circumventricular organs, namely the vascular organ of the lamina terminalis, the subfornical organ, the area postrema and the median eminence, brain structures characterized by a leaky blood-brain barrier. Furthermore, nuclear NF-IL6-IR was observed in the pituitary gland, the choroid plexus, the meninges as well as distinct large blood vessels throughout the entire brain. As for cellular phenotypes, we were able to demonstrate LPS-induced nuclear NF-IL6-IR in endothelial, microglial and ependymal cells, astrocytes, perivascular macrophages and neurons. Interestingly, the percentage of NF-IL6-reactive cells increased in parallel to the extend of late phases of the febrile response with a peak at 8h in most of the brain structures investigated. Conclusions- The present results suggest a role for NF-IL6 in the maintenance of LPS-induced fever rather than its initiation, which was hypothesized for STAT3 and NF\( \kappa \)B and even does not rule out the possibility of NF-IL6 being part of the mechanisms implicated in defervescence. The definite physiological significance of NF-IL6 activation and its participation in the manifestation of brain-controlled sickness type responses remain to be elucidated.