THE CENTRAL PYROGENIC ACTION OF INTERLEUKIN-6 IS RELATED TO NUCLEAR TRANSLOCATION OF STAT3 IN THE ANTEROVENTRAL PREOPTIC AREA OF THE RAT

T. Hübschle, E.-M. Harré, W. Meyerhof, U. Pehl, J. Roth and R. Gerstberger, Veterinary Physiology, Justus-Liebig-University, Frankfurter Str. 100, 35392 Giessen, Germany.

Central administration of the cytokine and endogenous pyrogen interleukin-6 (IL-6) elicits a variety of (patho-)physiological functions, such as the reduction of food intake and locomotor activity, the activation of the hypothalamo-pituitary-adrenocortical axis and the mediation of fever responses. The effects of IL-6 and related cytokines are mediated via the GP130 receptor family. Stimulation of these receptors activate a cytokine-specific signal transduction pathway, the so-called Janus kinase-signal transducer and activator of transcription (Jak-STAT) signalling cascade. IL-6 is known to act through the STAT3-isoform which gets phosphorylated, dimerizes and then translocates into the nucleus, where it regulates gene expression by binding to specific gene promoters, amongst others the promoter of the immediate early gene c-fos. This conversion of a cytokine stimulus into a long-term genetic action and its exact neuroanatomical location was studied previously in rats combining systemic and central IL-6 treatment with FOS-immunohisto-chemistry or FOS *in-situ* hybridisation technique. When thereby assessing putative central IL-6 target structures a specific FOS-activation pattern was found within the vascular organ of the lamina terminalis (OVLT), its adjacent medial preoptic area (MPO) and also ependymal layers of the ventricles and meninges. In order to demonstrate the central pyrogenic action of IL-6, adult male Wistar rats were applied with a lateral ventricular cannula that was stereotaxically inserted under general anaesthesia (100mg/kg ketamine and 10mg/kg xylazine). Then after a 10-12 days recovery period intracerebroventricular (icv) IL-6 bolus applications were performed with rat-recombinant IL-6 (100ng and 200ng in 5µl). Both IL-6 doses elicited a febrile response which was not observed in controls (5µl pyrogen free saline). The neuroanatomical basis of central IL-6 receptor activation on STAT3-proteins was investigated via central IL-6 stimulation combined with immunohistochemical procedures. Rats were perfused 15-90min after the icv stimulation, the brains were removed and analysed for STAT3-immunoreactivity which was additionally co-localised with the nuclear DAPI stain. In saline-treated animals constitutive STAT3-expression was low at all time points and predominantly detected within the cytoplasm of large cells within ventral aspects of the medio-caudal hypothalamus. In IL-6-treated rats an intense STAT3-expression and -translocation into cell nuclei was observed at 15-30min after icv treatment in various fore- and hindbrain sites. In particular, IL-6 induced a pronounced nuclear STAT3-translocation in the rostral hypothalamus, e.g. in the MPO and its ventromedial part and also in the lateral OVLT. The observed nuclear staining pattern was similar to that seen with FOS-analysis after IL-6 or endotoxin (LPS) treatment. The size and shape of the stained nuclei suggest that STAT3-immunoreactvity was predominantly located in neurons, but IL-6 also induced a prominent nuclear labelling in ependymal, meningeal and glial cells. Nuclear translocation of immunoreactive STAT3 therefore represents a novel and powerful tool to assess central IL-6 actions upstream of IL-6-induced c-fos gene activation. The results further support the importance of the OVLT and its adjacent preoptic area as main central IL-6 targets involved in the mediation of fever responses.

Thomas.Huebschle@vetmed.uni-giessen.de