PERIPHERALLY-RELEASED INTERLEUKIN-6 AND IMMUNE-TO-BRAIN SIGNALING IN MEDIATING LIPOPOYSACCHARIDE-INDUCED SICKNESS BEHAVIORS

Harden LM¹, du Plessis I¹, Roth J², Poole S³, and Laburn HP¹

¹) Brain Function Research Group, School of Physiology, University of the Witwatersrand, Johannesburg, South Africa 2) Department of Veterinary Physiology, Justus-Liebig-University, Giessen, Germany 3) Department of Endocrinology, National Institute for Biological Standards and Control, Potters Bar, United Kingdom.

Background - Peripherally-released interleukin (IL)-6, acting via the induction of cyclooxygenase (COX)-2 in the brain, has been strongly implicated as a critical endogenous mediator of fever induced by systemic and local lipopolysaccharide (LPS) administration. In contrast to the important role established for peripherally-released IL-6 in mediating LPS-induced fever, no clear role has emerged as yet for its involvement in mediating anorexia and lethargy, two brain-controlled sickness behaviors, also known to be induced with LPS administration. Using highly quantifiable measures of anorexia and lethargy, food intake and voluntary wheel running, we systematically investigated the contribution of peripherally-released IL-6 in mediating anorexia and lethargy induced by subcutaneous (s.c.) LPS administration. Procedure - Male Sprague-Dawley rats were randomly assigned to receive IL-6 antiserum (IL-6AS) (1.5 ml/rat) or pre-immune serum (1.5 ml/rat) intraperitoneally (i.p.) before receiving a s.c. injection of LPS (250 µg/kg) or saline. The efficacy of IL-6AS in decreasing the biological activity of IL-6 was assessed by measuring the levels of bioactive IL-6 in plasma. Results - Running activity and food intake of the rats was most reduced during day 1 after LPS administration and continued for at least 3 days. Pre-treating rats with IL-6AS significantly attenuated the magnitude of lethargy and anorexia on day 1 and significantly resolved the anorexia and lethargy faster, because from day 2 onwards rats injected with LPS and IL-6AS were running similar distances and consuming similar amounts of food to their pre-injection values and to rats injected with saline. Rats injected with LPS s.c. had a significant elevation in the biological activity of IL-6 in plasma compared to rats injected with saline. Pre-treating rats with IL-6AS significantly attenuated (by ~ 80%) the LPS-induced increase in biological activity of IL-6 in the plasma. Conclusions - Peripherally-released IL-6, possibility acting via the induction COX-2 or other cytokines such as IL-1β in the brain, appears to have an important role to play in mediating the duration of anorexia and lethargy induced by LPS administration. Identifying the physiological mechanisms involved in mediating the duration of anorexia and lethargy during illness is particularly relevant because it may enable the design of therapeutic interventions to oppose the detrimental effects of prolonging these sickness responses.