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Characterization of inflammation and immune cell modulation induced by low-dose LPS administration to healthy volunteers

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Human *in vivo* models of systemic inflammation are used to study the physiological mechanisms of inflammation and the effect of drugs and nutrition on the immune response. Although *in vivo* lipopolysaccharide (LPS) challenges have been applied as methodological tool in clinical pharmacology studies, detailed information is desired on dose-response relationships, especially regarding LPS hyporesponsiveness observed after low-dose *in vivo* LPS administration. A randomized, double-blind, placebo-controlled study was performed with single ascending low doses of LPS (0.5-2 ng/kg body weight) to assess the *in vivo* inflammatory effects of low intravenous LPS doses, and to explore the duration of the induced LPS hyporesponsiveness assessed by subsequent *ex vivo* LPS challenges in healthy volunteers. The *in vivo* inflammatory response showed a dose-dependent increase in body temperature, heart rate, CRP and circulating cytokines (TNF- α , IL-1 β , IL-6, IL-8) which showed clearly distinctive increases from placebo already at the lowest LPS dose level tested ($p \leq 0.0001$). *Ex vivo* LPS challenges were performed to estimate the duration and magnitude of LPS hyporesponsiveness by assessment of cytokine release. *In vivo* LPS administration dose-dependently induced a period of hyporesponsiveness in the *ex vivo* LPS-induced cytokine release, with maximal hyporesponsiveness observed at 6 hours, lasting no longer than 12 hours. For IL-6 and IL-8, indications for immune cell priming were observed. This study expands the knowledge about the dose-effect relationship of LPS-induced hyporesponsiveness. As such, the low-dose LPS challenge has been demonstrated to be a feasible methodological tool for future clinical studies exploring robust pharmacological or subtlenutritional immune-modulating effects.

Biography

Marlous Dillingh has a background in biomedical sciences. She is currently in training as a clinical pharmacologist at the Centre for Human Drug Research, Leiden, The Netherlands. Her main expertise is the integration of inflammation/immunology and pharmacology, applied in early phase clinical drug development, which is the focus of her PhD education.

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