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Short Communication

Single-trial conditioning in a human taste-endotoxin paradigm induces conditioned odor aversion but not cytokine responses

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ABSTRACT

Immunological responses to bacterial endotoxin can be behaviorally conditioned in rodents. However, it is unclear whether an acute systemic inflammatory response can be behaviorally conditioned in humans. Thus, in a double-blind placebo-controlled study, 20 healthy, male subjects received either a single injection of lipopolysaccharide (LPS) or saline together with a novel tasting beverage (conditioned stimulus, CS). Five days later, all subjects received a saline injection and were re-exposed to the CS. Blood was drawn prior to as well as 0.5, 1.5, 3, 4, 6, and 24 h after LPS administration or CS re-exposure. Endotoxin administration led to transient increases in plasma concentrations of interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)- α and to a significant rise in body temperature. Sole presentation of the CS during evocation did induce neither alterations in body temperature nor changes in plasma cytokine levels. However, subjects in the experimental group rated the smell of the CS significantly more aversive compared to the control group. Employing endotoxin as a US in a single trial taste-immune conditioning paradigm in humans shows a behaviorally conditioned smell aversion but no learned alterations in cytokine levels.

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1. Introduction

Behavioral conditioning of immune functions has been demonstrated by numerous studies in both animals and humans (Cohen et al., 1994; Schedlowski and Pacheco-Lopez, 2010). In animals, successful conditioning was shown for immunosuppression (Ader and Cohen, 1975; Exton et al., 2001), adaptive immune functions (Ader et al., 1993), and endotoxin-induced immune activation (Bull et al., 1991; Exton et al., 1995b; Janz et al., 1996) as well as endotoxin tolerance (Oberbeck et al., 2003). Administration of lipopolysaccharide (LPS, endotoxin), a complex glycolipid found in the outer membrane of gram-negative bacteria, is a safe and reliable model for the induction of an innate immune response in humans (Bahador and Cross, 2007). LPS injection transiently increases body temperature and the production and release of pro- and anti-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-10. Physical symptoms of increased innate immune activation induced by LPS like signs of sickness behavior and increases in body temperature, as well as the release

of cortisol and splenic norepinephrine or suppression of IL-2 production were successfully conditioned in rats in a taste aversion paradigm after a single pairing of LPS with saccharine solution as the CS (Exton et al., 1995a,c; Janz et al., 1996). In all these studies the behaviorally conditioned immune response was accompanied by a pronounced taste aversion against the CS. Human studies in which experimental immune activation was induced reported inconsistent results regarding a behaviorally conditioned immune activation. One study failed to behaviorally condition the response to interferon (IFN)- β 1a (Goebel et al., 2005), whereas another experiment successfully conditioned the prolongation of a cytokine-induced response to IFN- γ (Longo et al., 1999). In addition, an increase in the activity of natural killer cells could be behaviorally conditioned in one study, however, could not be replicated in a follow up experiment (Kirschbaum et al., 1992).

The aim of the present study was to analyze whether an innate immune response can be behaviorally conditioned in humans. In a double-blind, placebo-controlled approach we paired the injection of LPS (0.4 ng/kg of body weight) or an injection of saline as the unconditioned stimulus (US) with the ingestion of a novel tasting beverage as the CS. Five days after acquisition subjects were re-exposed to the CS during evocation, this time combined with a saline injection in all subjects. Blood was drawn at multiple time points before and after acquisition and

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