Available online at www.sciencedirect.com
ScienceDirect
Brain, Behavior, and Immunity 21 (2007) 301–307
BRAIN, BEHAVIOR, and IMMUNITY
www.elsevier.com/locate/ybrbi

Infection-induced proinflammatory cytokines are associated with decreases in positive affect, but not increases in negative affect

Denise Janicki-Deverts [a,*], Sheldon Cohen [a], William J. Doyle [b], Ronald B. Turner [c], John J. Treanor [d]

[a] *Department of Psychology, Carnegie Mellon University, Pittsburgh, PA, USA*
[b] *Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*
[c] *Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA, USA*
[d] *Infectious Diseases Unit, University of Rochester School of Medicine, Rochester, NY, USA*

Received 10 July 2006; received in revised form 6 September 2006; accepted 6 September 2006
Available online 18 October 2006

Abstract

Infection commonly triggers nonspecific psychological and behavioral changes including fatigue and malaise, anhedonia, inability to concentrate, and disturbed sleep that collectively are termed "sickness behaviors". Converging evidence from several lines of research implicate the activities of proinflammatory cytokines as a cause of sickness behaviors. Here we elaborate upon the findings of previous research by examining whether infection-associated elevations in local proinflammatory cytokines are associated with increased negative mood and decreased positive mood. One hundred and eighty-nine healthy adults were experimentally exposed to rhinovirus or influenza virus during a 6-day period of quarantine. Infection, objective signs of illness, nasal IL-1β, IL-6, and TNF-α, and self-reported affect were assessed at baseline and on each of the five post-challenge quarantine days. In the 153 persons who became infected following exposure to the challenge virus, daily production of IL-6, but not IL-1β or TNF-α, was associated with reduced concurrent daily positive affect. One-day lagged analyses showed that daily production of all three cytokines was related to lower positive affect on the next day. All lagged associations were independent of previous-day positive affect and objective signs of illness (mucus production, mucociliary clearance function). There were no associations between cytokines and negative affect. Findings support a causal association between pathogen-induced local cytokine production and changes in positive affect over a 24-h timeline.

Keywords: Influenza virus; Infection; Negative affect; Positive affect; Proinflammatory cytokines; Rhinovirus

1. Introduction

Infection commonly triggers nonspecific psychological and behavioral changes that collectively are termed "sickness behaviors" (Kent et al., 1992). Changes include experiences of fatigue and malaise, loss of interest in pleasurable activities such as eating and socializing, inability to concentrate, and disturbed sleep. Once thought merely to be a reactive response to the discomfort and debilitation of physical illness, sickness behavior now is suggested to play an integral role in the body's protective response to infection (Hart, 1988).

Converging evidence from several lines of research implicates the activities of proinflammatory cytokines as a cause of sickness behaviors (Kelley et al., 2003). For example, intraperitoneal injection of exogenous cytokines to laboratory rats produces behavioral changes consistent with sickness behavior such as suppressed food consumption (Sammut et al., 2001) and decreased social exploration (Bluthé et al., 1994). Similarly, research on human cancer patient populations showed that cytokine treatment is associated with sickness behaviors such as increased fatigue

* Corresponding author. Fax: +1 412 268 3294.
E-mail address: djanicki@andrew.cmu.edu (D. Janicki-Deverts).

0889-1591/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbi.2006.09.002

(Eskander et al., 1997; Rinehart et al., 1997), depressed mood (Capuron et al., 2001), and anorexia (Schiller et al., 1991).

Though suggestive of a role for cytokines in eliciting sickness behavior, the above studies are limited in that they may not accurately reflect proinflammatory processes initiated by a typical illness episode. An important limitation of the animal studies is that concentrations of injected cytokines far exceed cytokine levels that typically circulate during a chronic inflammatory reaction (Pollmacher et al., 2002). A similar argument can be made with regard to cytokine therapy, where dosages of administered cytokines often exceed physiologic levels typically associated with response to injury or infection.

Two recent studies examined the relation of cytokines to psychological and behavioral changes following exposure to mild pathogenic stimuli. In the first study, plasma cytokine levels, physical symptoms, sickness behavior, and psychological state were assessed 1, 3, and 9 h after intravenous administration of *Salmonella abortus equi* endotoxin or saline (Reichenberg et al., 2001). As expected, exposure to endotoxin, but not placebo, was associated with a significant increase in plasma IL-6 and TNF-α within 4 h, and with increased anxiety and depressed mood. Endotoxin-induced enhancement of anxiety and depressed mood showed a significant temporal correlation with observed increases in both proinflammatory cytokines. In a later study (Wright et al., 2005), administration of *S. typhi* vaccine, but not placebo, was associated with increased IL-6 concentrations, increased negative mood, and decreased positive mood within the first 3 h post-injection. Post-vaccination negative mood, but not positive mood, was correlated with the increase in IL-6.

In the present report, we elaborate upon these findings by testing the hypothesis that elevations in local (site of infection) cytokine production consequent to experimental infection with a viral upper respiratory pathogen (vURI) will be associated with alterations in self-reported affect. Though instantaneous reports of positive and negative affect tend to be strongly inversely correlated, there are circumstances under which individuals' experiences of positive and negative emotions can be partly independent of one another (e.g., Diener and Emmons, 1985; Watson et al., 1988). For example, when reflecting on the last day or week, one reasonably might report having been both happy and sad. There is also evidence that activation of separate cortical pathways may give rise to the experience of positive and negative emotion, with the former being related to the "approach" system and the latter to the "withdraw" system (Davidson, 1998). Given the experiential and proposed physiological independence of positive and negative affect, it is possible that proinflammatory cytokines relate differentially to positive and negative mood states. Reduced positive affect, or anhedonia, may be a direct effect of proinflammatory cytokine activity because consequent suppression in reward-seeking behaviors would allow energy to be shifted toward metabolic processes involved in fighting off infection. By comparison, elevated negative affect may be an indirect consequence of proinflammatory cytokine activity that arises as a response to the experience of cytokine-induced physical symptoms. This suggests that elevated local (nasal mucus) cytokines subsequent to viral infection will be associated with (1) increases in negative affect (NA) and (2) decreases in positive affect (PA), and that these associations occur for different reasons.

In separate models, we examined whether daily local (nasal) cytokine levels measured during experimental Influenza A virus or Rhinovirus 39 infections of adult humans predict increased NA and decreased PA on the same day and on the following day, and determined if any or all of the observed effects were independent of objective vURI signs (mucus weight and mucociliary clearance function). We included data from two different virus types to show that the association between cytokines and affect is consistent across virus types.

2. Method

We report a secondary analysis based on a large clinical trial designed to assess psychosocial predictors of resistance to viral infection. The design of the study involved an experimental model of upper respiratory virus infection that was employed by the second and third authors in a previous study of trait positive emotional style, average nasal cytokine levels, and illness expression (Doyle et al., 2006). Subjects were 95 men and 98 women, aged 21–55 years (mean age = 37.3, SD = 8.8), studied between 2000 and 2004 and experimentally exposed to one of two safety-tested upper respiratory viruses, Influenza A and rhinovirus 39 (RV39). Participants were recruited by newspaper advertisements soliciting subjects for an experimental study of the psychosocial risk factors that moderate viral upper respiratory infection and illness. The study was conducted in 11 cohorts of between 2 and 39 participants each.

Of the 193 subjects, 108 (56%) were white, 72 (37%) were black, and 13 (7%) indicated other racial/ethnic categories. The mean education was 13.8 years (SD = 2.2), 47% of subjects were smokers, and mean body mass index (BMI) was 29.0 (SD = 7.1). The study protocol was approved by the IRBs at the University of Pittsburgh and Carnegie Mellon University, all subjects provided written informed consent and were paid $820 for completing the study.

Potential subjects were screened by telephone and later interviewed and examined by a physician. To maximize the rate of infection, only subjects with an antibody titer to the challenge virus of $\leqslant 4$ were included. Subjects were excluded if they had a chronic medical condition, were not in generally good health, were pregnant or lactating, or had a recent or current upper respiratory infection. Individuals also were excluded if regularly taking medication, with exception of birth control, hormone replacement therapy, analgesics, and topical eczema/psoriasis medications.

Eligible participants who were exposed to RV39 were quarantined in a hotel for 1 day before and 5 days after viral challenge. Those who were exposed to Influenza A virus were quarantined for 1 day before and 6 days after challenge. To maintain comparability, we excluded the sixth day after challenge for those exposed to the Influenza A virus.

On each day of quarantine subjects received a general physical exam and a nasal wash with recovered fluids submitted for cytokine assay and virus culture. Subjects also were examined for objective signs of illness (mucus production and mucociliary clearance function; see Doyle et al., 2006), and completed questionnaire diaries that assessed subjective vURI symptoms (not discussed here), health practices, and moods. On the first day of quarantine and before virus exposure, female subjects received a pregnancy test. About 21 days post-quarantine subjects had blood drawn for assay of convalescent antibodies to the challenge virus.