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Circadian rhythmicity, variability and correlation of interleukin-6 levels in plasma and cerebrospinal fluid of healthy men

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Summary
Background: Interleukin-6 (IL-6) is a cytokine with pleiotropic actions in both the periphery of the body and the central nervous system (CNS). Altered IL-6 secretion has been associated with inflammatory dysregulation and several adverse health consequences. However, little is known about the physiological circadian characteristics and dynamic inter-correlation between circulating and CNS IL-6 levels in humans, or their significance.
Methods: Simultaneous assessment of plasma and cerebrospinal fluid (CSF) IL-6 levels was performed hourly in 11 healthy male volunteers over 24 h, to characterize physiological IL-6 secretion levels in both compartments.
Results: IL-6 levels showed considerable within- and between-subject variability in both plasma and CSF, with plasma/CSF ratios revealing consistently higher levels in the CSF. Both CSF and plasma IL-6 levels showed a distinctive circadian variation, with CSF IL-6 levels exhibiting a main

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24 h, and plasma a biphasic 12 h, circadian component. Plasma peaks were roughly at 4 p.m. and 4 a.m., while the CSF peak was at around 7 p.m. There was no correlation between coincident CSF and plasma IL-6 values, but evidence for significant correlations at a negative 7—8 h time lag.
Conclusions: This study provides evidence in humans for a circadian IL-6 rhythm in CSF and confirms prior observations reporting a plasma biphasic circadian pattern. Our results indicate differential IL-6 regulation across the two compartments and are consistent with local production of IL-6 in the CNS. Possible physiological significance is discussed and implications for further research are highlighted.
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1. Introduction

Interleukin-6 (IL-6) is a 184 amino acid cytokine discovered three decades ago as a protein involved in B-cell differentiation (Hirano et al., 1986). However, IL-6 is a far more versatile peptide, influencing numerous cell types and being responsible for a plethora of pro- and anti-inflammatory immune functions, as well as metabolic, endocrine, autocrine and paracrine effects in humans (Mihara et al., 2012; Papanicolaou and Vgontzas, 2000; Scheller et al., 2011; Spooren et al., 2011). The pleiotropic biology of IL-6 is mediated through a number of different signal transduction pathways (Heinrich et al., 2003; Rose-John and Heinrich, 1994).

In the periphery, IL-6 is produced by immune or immune-accessory cells, non-immune endocrine and endothelial cells, as well as white adipose tissue and skeletal muscle (Mohamed-Ali et al., 1997; Vgontzas et al., 1999). Its expression is stimulated by sympathetic nervous system activity, catecholamine production, and other cytokines, while suppressed by glucocorticoids and estrogens (Mohamed-Ali et al., 2001; Papanicolaou et al., 1996a; Sanceau et al., 1995; Vicennati et al., 2002; Zhou et al., 1993). IL-6 plays a central role in immune responses by regulating acute-phase reactions, host defense mechanisms and haematopoiesis, angiogenesis, thyroid function, and the hepatic synthesis and secretion of C-reactive protein (CRP) (Akira et al., 1993; Castell et al., 1989; Heinrich et al., 1990; Mihara et al., 2012). Furthermore, IL-6 stimulates osteoclastogenesis and intermediary metabolism and regulates lipid metabolism and endothelial function (Akira et al., 1993; Keller et al., 1996; Manolagas and Jilka, 1995; Stouthard et al., 1995).

In the CNS, IL-6 is produced by microglial cells, astrocytes and neurons. Stimuli of IL-6 production are very diverse, including a broad spectrum of neurotransmitters, neuropeptides, cytokines, pathogens or neuronal depolarization (Gruol and Nelson, 1997; Spooren et al., 2011; Van Wagoner et al., 1999). CNS IL-6 is considered a neurotrophic factor targeting overall homeostasis and development of the nervous system (Spooren et al., 2011). CNS IL-6 plays a crucial role in the maintenance of blood—brain-barrier integrity and is a key player in mediating pleitropic effects on astrocytes and microglia (Fee et al., 2000; Gruol and Nelson, 1997; Marz et al., 1999; Spooren et al., 2011; Streit et al., 2000; Swartz et al., 2001; Tilgner et al., 2001). IL-6 may, thus, play an important role in the complex autonomic, psychoneuroendocrine and metabolic interplay of inflammation in the CNS (Helwig et al., 2008; Spooren et al., 2011).

A growing body of research suggests that IL-6 functions as a stress biomarker. Elevated plasma IL-6 levels have repeatedly been reported in response to physical and psychological stress and altered IL-6 secretion has been frequently associated with a variety of health consequences through stress-immune system dysregulation (Chourbaji et al., 2006; Chrousos, 1995; Elenkov et al., 2005; Steptoe et al., 2007; Sternberg, 2001). While acute stress-induced IL-6 increases might be useful in maintaining homeostasis, a long-term IL-6 increase is indicative of chronic stress and unfavorable health outcomes (Hansel et al., 2010).

IL-6, thus, appears to have a key role mediating a rapid interplay between immune system and CNS function. However, the relation between peripheral versus central IL-6 has not been thoroughly investigated. Prior study results suggested circadian and even ultradian variations of circulating IL-6 concentrations, with generally lower levels during daytime and higher during the night (Bauer et al., 1994; Crofford et al., 1997; Gudewill et al., 1992; Izawa et al., 2013b; Kanabrocki et al., 1999; Lissoni et al., 1998; Perry et al., 2009; Redwine et al., 2000; Sothern et al., 1995a; Vgontzas et al., 1999, 2002, 2005), while disturbed day—night cycles and sleep deprivation affect these rhythmic oscillations (Redwine et al., 2000; Vgontzas et al., 1999, 2002, 2003). However, less is known about the regulation of IL-6 release in the brain under physiological conditions, or about the dynamic interplay between plasma and CSF IL-6 levels in humans across a 24 h period. Some prior studies that have shown no significant correlation between CSF and plasma IL-6 levels have proposed differential regulation mechanisms of IL-6 in CNS and the periphery (Lindqvist et al., 2009; Stenlof et al., 2003), but this has been studied little.

The main objective of the present study was the precise and simultaneous examination of sequential 24 h plasma and CSF IL-6 measurements, with a primary goal of defining IL-6 circadian secretion patterns and to elucidate relations, if any, between peripheral and CNS IL-6 concentrations in healthy male volunteers.

2. Methods

2.1. Subjects

We collected data from 11 healthy male, U.S. civilian study volunteers, who participated in a serial CSF and plasma sampling study approved by the Institutional Review Board of the University of California, San Diego Medical Center and the Research Committee of the San Diego Veterans Affairs Medical Center. One of the volunteers had only a single CSF sample and was excluded from analysis. The 10 remaining participants were mentally healthy, having met study