Low-dose endotoxemia and human neuropsychological functions

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Abstract

Epidemiological data demonstrate an association between systemic low-grade inflammation defined as 2- to 3-fold increases in circulating inflammatory mediators and age-related decline in cognitive function. However, it is not known whether small elevations of circulating cytokine levels cause direct effects on human neuropsychological functions. We investigated changes in emotional, cognitive, and inflammatory parameters in an experimental in vivo model of low-grade inflammation. In a double-blind crossover study, 12 healthy young males completed neuropsychological tests before as well as 1.5, 6, and 24 h after an intravenous injection of Escherichia coli endotoxin (0.2 ng/kg) or saline in two experimental sessions. Endotoxin administration had no effect on body temperature, cortisol levels, blood pressure or heart rate, but circulating levels of tumor necrosis factor (TNF) and interleukin (IL)-6 increased 2- and 7-fold, respectively, reaching peak values at 3 h, whereas soluble TNF-receptors and IL-1 receptor antagonist peaked at 4.5 h. The neutrophil count increased and the lymphocyte count declined. In this model, low-dose endotoxemia did not affect cognitive performance significantly but declarative memory performance was inversely correlated with cytokine increases. In conclusion, our findings demonstrate a negative association between circulating IL-6 and memory functions during very low-dose endotoxemia independently of physical stress symptoms, and the hypothalamo–pituitary–adrenal axis.

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Keywords: Endotoxin; Inflammation; Cognitive function; Cytokines

1. Introduction

Accumulating data suggest that circulating cytokines affect human brain function. Cytokines are likely to be centrally involved in the pathogenesis of so-called sickness behavior, accompanying severe acute infections. However, it is not yet known whether low-grade increases in circulating cytokine levels, characterizing many chronic diseases, influence brain functions (Pollmacher et al., 2002).

Systemic low-grade inflammation is defined by a 2- to 3-fold increase in inflammatory cytokines and acute phase proteins (Petersen and Pedersen, 2005; Ross, 1999). Several reports have confirmed an association between systemic low-grade inflammation on the one hand and increasing age and chronic disorders such as the metabolic syndrome, type 2 diabetes, and atherosclerosis on the other (Barzilay et al., 2001; Duncan et al., 2003; Fest et al., 2002; Ford, 2002; Freeman et al., 2002; Han et al., 2002; Lindsay et al., 2002; Nakanishi et al., 2002; Pradhan et al., 2001; Vozarova et al., 2002).

In addition, epidemiological studies suggest that systemic low-grade inflammation may be involved in the pathology of age-associated cognitive decline, including...
both Alzheimer’s disease (AD) and vascular dementia (Krabbe et al., 2004). Yaffe et al. (2003, 2004) have thus shown a strong association between baseline levels of inflammation in elderly subjects aged 70–79 and later cognitive decline (after 2 and 5 years of follow-up) and cross-sectional studies have consistently found associations between low-grade systemic inflammation and dementia (Alvarez et al., 1996; Bruunsgaard et al., 1999; Engelhart et al., 2004; Licastro et al., 2000).

There is an ongoing debate as to whether peripheral cytokine elevations found in relation to cognitive impairment are a causative agent in cognitive decline or whether they represent spillover from inflammatory processes in the CNS (Krabbe et al., 2004). Thus, the association between aging and systemic low-level inflammation could, in part, be related to plaque formation in the brain. Nevertheless, it is also possible that the brain responds to inflammation elsewhere as some cytokines such as TNF-α are known to be able to cross the blood–brain barrier (BBB) and to interact with the CNS via receptors in afferent neurons (Pan and Kastin, 2004; Tracey, 2002). In favor of this hypothesis, studies in which severely ill patients received cytokines in high doses demonstrated that cytokine administration produced behavioral alterations (Meyers, 1999). However, in these clinical studies high doses of cytokines might interfere with the pre-existing disease state and an evaluation of the isolated effects of cytokines on human brain function has not been possible (Pollmacher et al., 2002). Thus, it is desirable to investigate the emotional and cognitive effects of peripheral inflammation in healthy humans in more controlled models. An experimental model for sepsis has been developed using an intravenous bolus injection of purified Escherichia coli or Salmonella abortus equi endotoxin (Elin et al., 1981). Administration of S. abortus equi endotoxin (0.8 ng/kg body weight) to healthy young subjects resulted in negative effects on verbal and non-verbal declarative memory functions (Cohen et al., 2003; Reichenberg et al., 2001) and depression score (Reichenberg et al., 2001) but also in an improvement in working memory (Cohen et al., 2003). These findings point towards a subtly regulated system with differential effects of endotoxia/inflammatory mediators on different cognitive functions. Although, subjects did not experience any of the classical symptoms of endotoxia in these studies, they developed an increase in body temperature of 0.5°C as well as approximately 100-fold increases in plasma cytokines (TNF-α, IL-6, and IL-1 receptor antagonist (Ra)), thus representing a model that does not mimic systemic low-grade inflammation in aging and chronic disease. Furthermore, the hypothalamo–pituitary–adrenal (HPA) axis was activated which was reflected by elevated levels of cortisol. To test the hypothesis that brain function is affected by inflammation outside the CNS (such as inflammation elicited by infections or chronic diseases) we have developed a model of systemic low-grade inflammation in which lower doses of E. coli endotoxin (0.06–0.2 ng/kg) are administered (Krogh-Madsen et al., 2004; Starkie et al., 2003). The latter model (0.2 ng/kg) induces a 2- to 10-fold increase in plasma TNF-α and IL-6 without inducing a temperature response or an activation of the HPA axis. In the present study, we therefore applied the 0.2 ng/kg endotoxin model to investigate if acute elevations of plasma cytokines to levels similar to those seen in individuals with low-grade systemic inflammation would have negative effects on emotional and memory functions in young healthy volunteers.

2. Materials and methods

2.1. Volunteers

Twelve healthy young men (mean age 26 years (range 21–29), mean years of education 14.7 (range 12–18), mean BMI 24 (range 21–27)) participated in the study. All participants gave written informed consent. Before the experiments, all subjects underwent a thorough clinical examination. All subjects had a negative medical history and physical examination revealed no abnormalities.

Blood analyses showed normal hemoglobin, white blood cell count (WBC), WBC subsets, CRP, blood-glucose, Na, K, kidney parameters, liver function, and coagulation parameters. All had a normal electrocardiogram (ECG). The volunteers did not use any medication, and urine was without glucose, albumin, ketones, and leukocytes. All subjects practised exercise on a regular basis, no more than four times a week.

Exclusion criteria were: presence of any medical or psychiatric illness, BMI > 30, febrile illness or travels outside of Europe/North America in the month preceding the study, vaccination in the month preceding the study, present use of drugs other than alcohol, and less than 7 years of education.

As a part of the initial screening, all subjects passed a neuropsychological testing session identical to the sessions on the experimental day(s). Furthermore, they all underwent the Raven Advanced Progressive Matrices test, quick version, validated for Danes, which is considered as a good measure of general intelligence. All subjects had a normal score.

2.2. Study design

The study had a balanced, randomized, double-blind, crossover design.

Subjects arrived at the research unit between at 07:00 and 07:45 h. Their residence was close to the research unit (median 2.55 km; range 0.3–7 km) and to get to the laboratory they were instructed to walk, take public transporta-
tion, or a short city ride by bike with low-intensity corresponding to a short walk. Upon arrival they rested for at least 1 h to eliminate any potential acute effect of exercise. Following this period of rest and adaptation to the environment, baseline blood samples were collected and subjects underwent baseline emotional (visual analogue mood scale, VAMS) and neuropsychological testing. An intravenous bolus of saline (isotonic NaCl) or endotoxin (Endotoxin E. coli, Lot EC-6, United States Pharmacopeia Convention, Rockville, MD) was administered immediately afterwards (between 8:30 and 9:15 AM). Endotoxin dose was of 0.2 ng/kg body weight. The emotional and neuropsychological testing series were repeated three times postinjection: at time points 1.5–2, 5.5–6, and 23.5–24 h. Neuropsychological testing was conducted by a medical doctor in a clinical research unit under the supervision of a neuropsychologist.

The neuropsychological test battery assessed memory, and learning, working memory and executive functions, attention and motor speed. Memory and learning were assessed using a word-list learning test. In the learning condition, subjects are requested to immediately repeat a 15 word-list. This procedure is repeated three consecutive times. In the delayed memory condition, subjects are requested to repeat the list, again, from memory after a 20 min delay filled with other tests. The total number of correct verbatim recall was counted. The Letter–Number Sequencing and Digit Span backward (Wechsler Memory Scale III) were used to assess working memory. The number of correct responses was counted. Attention and motor speed were assessed using the digit span forward and digit symbol coding tests (Wechsler Adult Intelligence Scale III). The number of correct responses was counted. Executive functions were assessed using the Trails Making Test (TMT) A and B the time needed to complete the test was recorded. Eight parallel test versions were used, so each subject was administered a different version on each of the four testing periods in each of the two testing sessions. The order in which the different test versions were administered was counterbalanced across subjects to avoid any non-random version-dependent bias. The individual tests were presented in a fixed order in all eight versions. Test–retest correlations were >.64 for all measures and alternate form reliability were >.55 for all measures (Spreen and Strauss, 1988; The Psychological Corporation, 1997). Emotional state was assessed after each neuropsychological testing using the VAMS.

Self-reported physical sickness symptoms (headaches, muscle pain, shivering, nausea, breathing difficulties, and fatigue) were assessed at the end of each testing period, by a questionnaire using a 10-point Likert scale (0, no symptoms; 9, very severe symptoms).

The study was approved by the Scientific Ethical Committee of Copenhagen and Frederiksberg Municipalities [jr. no. (KF) 11–032/02].

2.3. Blood sampling and cytokine analyses

Blood was drawn at $t = 0, 1.5, 3, 4.5, 6, and 24$ h for white blood cell (WBC) counts and hemoglobin as well as for isolation of serum and plasma. Blood samples were drawn into ice-cold tubes containing EDTA and centrifuged immediately thereafter. Plasma for cytokine detection was stored at $-80$ °C until analyzed. The following cytokines were determined by the enzyme-linked immunosorbent assay (ELISA) technique (R&D Systems, Minneapolis, MN): TNF-α (detection limit 0.5 pg/ml), sTNF-receptor I (sTNF-R) (7.8 pg/ml), IL-6 (0.156 pg/ml), and IL-1 receptor antagonist (IL-1Ra) (46.9 pg/ml). All ELISA kits were from R&D Systems, Minneapolis, MN, USA. All cytokine determinations were measured in duplicates and mean values were calculated. Plasma concentrations of cortisol were measured by ELISA technique (DSL, Webster, TX) at time points 0, 6, and 24 h.

Standard laboratory procedures were employed for WBC counts.

2.4. Statistics

Statistical analyses were performed using SAS statistical software v8 (SAS Institute, Cary, NC, USA). Initial analyses revealed that concentrations of cytokines were not normally distributed. Therefore, these parameters were log transformed and geometrical means given. Absolute changes in parameters following endotoxin administration were evaluated by an analysis of variance (ANOVA) for repeated measurements (model parameter = time + treatment + time × treatment). If a significant interaction (time × treatment) was found, a paired $t$ test was used to detect differences between saline and endotoxin values. Correlations were calculated using Pearson’s correlations coefficient. In all tests $p < .05$ was considered significant.

3. Results

Heart rate, blood pressure, and temperature remained unchanged after endotoxin injection and subjects did not complain about adverse effects (e.g., headache, chills, nausea, and muscle soreness).

Endotoxin administration induced highly significant changes in plasma concentrations of TNF-α ($F(5,53) = 3.15, p = .015$ for a treatment by time interaction), IL-6 ($F(5,50) = 5.58, p = .0002$ for a treatment by time interaction), sTNF-R ($F(5,55) = 4.74, p = .0011$ for a treatment by time interaction) and IL-1Ra ($F(5,51) = 10.14, p < .0001$ for a treatment by time interaction) compared to saline (Fig. 1).

Specifically, plasma TNF-α and IL-6 increased 2- and 7-fold, respectively, reaching peak values at 3 h, whereas
IL-1Ra peaked at 4.5h with an increase of 9-fold. The concentrations of sTNF-R were only slightly increased at time points 3 and 4.5h. Plasma IL-1β was only measured in a small fraction of the samples as it was below detection limit at baseline. It became detectable at 3–4.5h (levels of 0.14–0.49 pg/ml) and was undetectable at 24h in all samples (data not shown). The neutrophil count increased ($F(5,43) = 27.62, p < .0001$ for a treatment by time interaction) and the lymphocyte count declined ($F(5,43) = 3.50, p = .0096$ for a treatment by time interaction) in response to endotoxin administration (Table 1). Cortisol levels did not differ between endotoxin and saline days (Table 1).

Overall, a diurnal rhythm was found in declarative memory assessed by the word-list learning test, in that subjects showed decreasing scores throughout the day, recovering after 24h (for the delayed condition ($F(3,30) = 10.85, p < .0001$), immediate recall condition ($F(3,30) = 5.26, p = .005$)). During the endotoxin session, subjects showed less diurnal variation in the immediate condition of this test, i.e., an improved declarative memory performance relative to the saline session, however, the difference between the groups did not reach statistical significance ($F(3,30) = 2.11, p = .12$ for a treatment by time interaction) (Fig. 2). Descriptive analysis using paired $t$ test revealed a tendency to better performance under endotoxin conditions at $t = 6h$ ($t(11) = -1.955, p = .077$) (Fig. 2).

Low-dose endotoxemia did not affect performance on tests of working memory, executive functions, attention

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**Table 1**

Concentrations of lymphocytes, neutrophils, and cortisol in humans following administration of either 0.2 ng/kg BW E. coli endotoxin or saline

<table>
<thead>
<tr>
<th>Hours from baseline</th>
<th>Endotoxin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.76 (0.46)</td>
<td>1.85 (0.52)</td>
</tr>
<tr>
<td>1.5</td>
<td>1.62 (0.45)</td>
<td>1.81 (0.60)</td>
</tr>
<tr>
<td>3</td>
<td>1.39 (0.46)*</td>
<td>1.86 (0.62)</td>
</tr>
<tr>
<td>4.5</td>
<td>1.41 (0.60)*</td>
<td>1.97 (0.75)</td>
</tr>
<tr>
<td>6</td>
<td>1.55 (0.49)*</td>
<td>1.97 (0.74)</td>
</tr>
<tr>
<td>24</td>
<td>1.83 (0.66)</td>
<td>2.10 (0.78)</td>
</tr>
</tbody>
</table>

**Lymphocytes**

**Neutrophils**

<table>
<thead>
<tr>
<th>Hours from baseline</th>
<th>Endotoxin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.30 (0.56)</td>
<td>2.44 (0.94)</td>
</tr>
<tr>
<td>1.5</td>
<td>2.53 (0.73)</td>
<td>3.08 (1.56)</td>
</tr>
<tr>
<td>3</td>
<td>4.56 (2.21)*</td>
<td>3.03 (1.26)</td>
</tr>
<tr>
<td>4.5</td>
<td>6.98 (1.55)*</td>
<td>2.93 (1.02)</td>
</tr>
<tr>
<td>6</td>
<td>5.51 (1.35)*</td>
<td>3.11 (0.99)</td>
</tr>
<tr>
<td>24</td>
<td>2.19 (0.55)</td>
<td>2.70 (0.92)</td>
</tr>
</tbody>
</table>

**Cortisol**

<table>
<thead>
<tr>
<th>Hours from baseline</th>
<th>Endotoxin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13.5 (3.0)</td>
<td>14.7 (4.9)</td>
</tr>
<tr>
<td>1.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>7.3 (1.7)</td>
<td>7.3 (1.7)</td>
</tr>
<tr>
<td>24</td>
<td>12.8 (4.1)</td>
<td>14.0 (3.7)</td>
</tr>
</tbody>
</table>

Values are means ± standard deviations. Units are 10^9/ml for lymphocytes and neutrophils; µg/dl for cortisol.

* Denotes significant difference from saline values (paired $t$ test).
or motor speed. Furthermore, no difference in emotional parameters (VAMS) was detected.

To correlate cytokine changes to changes in the word-list learning, a new parameter was computed, representing the decrease in performance during the endotoxin day in the third testing period \((t = 5.5–6\ h)\) minus the decrease in performance during saline day at the same point in time. There was a negative correlation between increases in plasma concentrations of IL-6 at 4.5 and 6 h and the word-list learning performance in the third testing period \((r_D < 0.73, p < .01\) and \(r_D < .64, p < .05\), respectively), so that subjects with small increases in IL-6 performed better than subjects with larger increases (Fig. 3). This pattern repeated itself with sTNF-R also at \(t = 4.5\) and 6 h in relation to the word-list learning at 6 h \((r = -.5, p < .1\) and \(r = -.56, p = .07\), and a tendency to the same was seen with TNF-\(\alpha\) at \(t = 4.5\ h\) in relation to the word-list learning at 6 h \((r = -.57, p = .07\). No significant correlations were found between IL-1Ra and the word-list learning performance. A backward stepwise regression including IL-6, sTNF-R and TNF-\(\alpha\) values at \(t = 4.5\) and 6 h yielded a model that included only IL-6 levels at \(t = 4.5\ h\) \((p = .017)\).

4. Discussion

In the present study a human experimental model of systemic low-grade inflammation was developed. We sought to determine whether acute systemic low-grade inflammation without any detectable physical stress symptoms would induce changes in cognitive function. Subjects developed consistent, but slight increases in plasma concentrations of TNF-\(\alpha\), sTNF-R, IL-6, and IL-1Ra without activation of the HPA axis. The levels of inflammatory mediators obtained during endotoxemia were comparable with levels observed in normal human aging as well as in patients with type 2 diabetes or atherosclerosis (Krabbe et al., 2004; Petersen and Pedersen, 2005). Furthermore, we found clear signs of inflammation as represented by a shift in concentrations of leukocyte subpopulations. Contrary to our hypothesis, we found that acute systemic low-grade inflammation did not result overall in decreased performance on cognitive parameters. However, performance in declarative memory was inversely correlated with increases in IL-6 and sTNF-R, and marginally to increases in TNF-\(\alpha\), indicating a negative effect of systemic low-level inflammation on some areas of cognitive function.

The findings of endotoxin-induced low-grade elevations in circulating cytokines without a detectable activation of the HPA axis and without an increase in body temperature are in accordance with previous findings in our group (Krogh-Madsen et al., 2004) as well as with findings by others (Mullington et al., 2000). Consistent with our findings, it has, furthermore, recently been reported that administration of a somewhat higher dose of endotoxin \((0.8\ ng/kg)\) to healthy young volunteers produces a significant impairment in declarative memory that is correlated with levels of TNF-\(\alpha\) (Reichenberg et al., 2001). The latter model also induces significant improvement in working memory (Cohen et al., 2003), an increase in depressive symptoms (Reichenberg et al., 2001) but, in contrast to the present data, it involves also an activation of the HPA axis. In accordance with our data, lower doses of Salmonella endotoxin \((0.2\ ng/kg)\) cause increases in TNF-\(\alpha\) and IL-6 to approximately 40 pg/ml that are accompanied by an increase in non-REM sleep amount and intensity without activation of the HPA axis or increase in body temperature.
Nevertheless, active transport mechanisms through the BBB have been documented for IL-1, TNF-α, and IL-1ra (Wilson et al., 2002), and other studies indicate that IL-6 can cross the human BBB during non-pathological conditions and pathological conditions (Moller et al., 2002). The barrier function of the BBB decreases with age, in AD, and in response to elevated levels of TNF-α, IL-1β, and IL-6. (Garton et al., 1991; Mattila et al., 1994; Pan and Kastin, 2004), making the passage of cytokines possible, but this does not explain the present observations in young healthy volunteers. Moreover, direct communication pathways between peripheral cytokines and the CNS have been described. Thus, afferent neurons respond to cytokine stimulation directly (Dantzer et al., 1998), and stimulation of the efferent vagus nerve inhibits the production of TNF-α in liver, spleen and heart, and attenuates serum concentrations of TNF-α during endotoxemia (Tracey, 2002). Models of acute brain injury have demonstrated that IL-1 can cause neurodegeneration whereas it is controversial if cytokines such as TNF-α and IL-6 are mainly neurotoxic (based largely on acute interventions) or neuroprotective (based largely on studies on genetically modified animals) and it is probable that cytokines can both enhance and inhibit neuronal injury depending on the time course and extent of expression (Allan and Rothwell, 2001). However, cytokines are also necessary for normal cognitive functions and they exert their effects on the brain in a nonlinear fashion, as proposed for some sleep and memory functions (Avital et al., 2003; Pollmacher et al., 2002; Yirmiya et al., 2002). Thus, it seems plausible that, similarly to the association between psychological stress and cognitive functions, a bell-shaped or inverted “U” shaped correlational relationship exists between cytokine concentrations and brain functions. Accordingly, different doses of endotoxin seem to have beneficial or detrimental effects on specific forms of memory—i.e., very low doses, such as those administered in the present study, might improve declarative memory and do not affect working memory, somewhat higher doses impair declarative memory but improve working memory (Cohen et al., 2003; Reichenberg et al., 2001). Although not tested in a model of endotoxemia in humans, higher doses probably impair all types of memory as indicated by studies in which cancer patients have received cytokine therapy (Meyers, 1999) and by animal studies (Pugh et al., 1998; Shaw et al., 2001). Inflammatory cytokines seem to be associated with less improvement or more impairment in declarative memory, but not with changes in working memory, which may depend on other mechanisms (Cohen et al., 2003). During low-dose endotoxemia in the present study, we found that IL-6 was the cytokine with the strongest association to changes in declarative memory functions, and levels of IL-6 previous to the third testing period predicted performance in declarative memory. It is possible that IL-6 is a key mediator of some of the effect on declarative memory function observed during very low-dose endotoxemia, but this needs further investigation. Thus, production of different cytokines is strongly interrelated. Although IL-6 may be the best biomarker of the response in the neuro-immune interface this does not necessarily reflect that it also is the most important biological driver on a mechanistic level.

Limitations of the present design should be considered. The test–retest correlations for the neuropsychological test battery are relatively low, and it is possible that the lack of significant differences reflects a power-problem. Also, the present design aimed to model how the brain reacts to systemic inflammation, that is, inflammation outside the brain, and not conditions as AD with substantial inflammation in the brain. Furthermore, in the present study endotoxin was administered to young subjects and their response cannot necessarily be extrapolated to subjects with chronic systemic low-grade inflammation or aged subjects. It is also likely that acute and chronic elevations of cytokines may have different effects on brain functions. Physical exercise with high intensity and for a long duration results in high plasma levels of IL-6 that blunt the TNF response to a low-dose of endotoxin (Starkie et al., 2003). In the present study, subjects were allowed to perform a short walk or a short, low-intensity city ride by bike as mode of transportation to the experimental unit in the morning, which might potentially have affected their proinflammatory response. However, this is unlikely as subjects lived very close to the laboratory; they performed very low-intensity physical activity for a short duration; they rested for at least 1 h before baseline values were obtained; and, most importantly, plasma levels of IL-6 were stable throughout the day in the saline experiments. The subjects were not sedentary, but to our knowledge, there is no evidence that physical training status affects the cytokine response to endotoxin.

In conclusion, in a human in vivo endotoxemia model, low-grade increases in concentrations of circulating cytokines are inversely associated to declarative memory performance independently of physical stress symptoms and of the HPA axis, thus adding further evidence pointing towards inflammatory mediators playing a role in the modulation of brain functions.

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References


