Brain, Behavior, and Immunity 38 (2014) 202–210

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Postoperative cognitive dysfunction: Involvement of neuroinflammation and neuronal functioning

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ARTICLE INFO

Article history:
Received 6 November 2013
Received in revised form 27 January 2014
Accepted 3 February 2014
Available online 8 February 2014

Keywords:
Postoperative cognitive dysfunction
Surgery
Learning and memory
Exploratory behavior
Neuroinflammation
Brain-derived neurotrophic factor
Neurogenesis

ABSTRACT

Postoperative cognitive dysfunction (POCD) has been hypothesized to be mediated by surgery-induced inflammatory processes, which may influence neuronal functioning either directly or through modulation of intraneuronal pathways, such as the brain derived neurotrophic factor (BDNF) mediated pathway.

To study the time course of post-surgical (neuro)inflammation, changes in the BDNF-pathway and POCD, we subjected 3 months old male Wistar rats to abdominal surgery and implanted a jugular vein catheter for timed blood sampling. Cognition, affective behavior and markers for (neuro)inflammation, BDNF and neurogenesis were assessed at 1, 2 and 3 weeks following surgery.

Rats displayed changes in exploratory activity shortly after surgery, associated with postoperatively elevated IL-6 plasma levels. Spatial learning and memory were temporarily impaired in the first 2 weeks following surgery, whereas non-spatial cognitive functions seemed unaffected. Analysis of brain tissue revealed increased neuroinflammation (IL-1B and microgliosis) 7 days following surgery, decreased BDNF levels on postoperative day 14 and 21, and decreased neurogenesis until at least 21 days following surgery.

These findings indicate that in young adult rats only spatial learning and memory is affected by surgery, suggesting hippocampal dependent cognition is especially vulnerable to surgery-induced impairment. The observed differences in time course following surgery and relation to plasma IL-6 suggest cognitive dysfunction and mood changes comprise distinct features of postoperative behavioral impairment. The postoperative changes in neuroinflammation, BDNF and neurogenesis may represent aspects of the underlying mechanism for POCD. Future research should be aimed to elucidate how these players interact.

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1. Introduction

Following illness or trauma, patients may experience cognitive impairment. One event that has been associated with cognitive decline is surgery (Newman et al., 2007; Rasmussen, 2006). Postoperative cognitive dysfunction (POCD) involves a wide range of cognitive functions including working memory, long term memory, information processing, attention and cognitive flexibility (Hovens et al., 2012), adversely affecting quality of life, social dependence, and mortality (Steinmetz et al., 2009). In most cases, cognitive function returns to normal within a month after surgery, but in some patients the cognitive decline persists (Rasmussen, 2006). Although POCD can occur at all ages, the main risk factor for POCD is advanced age (Krenk et al., 2010; Monk et al., 2008). Other risk factors include the severity and duration of the surgical procedure (Krenk et al., 2010).

The pathogenesis of POCD remains largely unknown. Evidence is accumulating for a key role of inflammation in the disease process (Krenk et al., 2010). Local inflammation due to the surgical trauma is paralleled by an increase in systemic inflammatory mediators (Beloosesky et al., 2007; Cibelli et al., 2010; Ramlawi et al., 2006; Shapira-Lichter et al., 2008; Yaffe et al., 2003) Several of these mediators have been shown to influence inflammatory processes in the brain, leading to the activation of microglia, the immune cells of the brain, and the concurrent endogenous production of pro-inflammatory cytokines (Cibelli et al., 2010; Dilger and Johnson, 2008; Ji et al., 2013; Tang et al., 2011; Wan et al., 2007).

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http://dx.doi.org/10.1016/j.bbi.2014.02.002
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Since neuroinflammation has been associated with impaired cognitive functioning, this mechanism is hypothesized to underlie POCD development (Cibelli et al., 2010; Hovens et al., 2012; Wan et al., 2007). Aging has been associated with an exacerbated inflammatory response and more pro-inflammatory profile (Barrientos et al., 2006; Cortese et al., 2011; Dilger and Johnson, 2008), which may account for the increased incidence of POCD in the elderly (Barrientos et al., 2012; Beloosesky et al., 2007; Hudetz et al., 2007; Ramlawi et al., 2006; Wan et al., 2007; Yaffe et al., 2003). In addition to a direct effect of pro-inflammatory cytokines, such as IL-1B and IL-6, on neuronal functions essential for learning and memory, inflammatory factors may also indirectly influence neuronal functioning (Yirmiya and Goshen, 2011). In particular brain-derived neurotrophic factor (BDNF) and its intraneuronal pathway have been implicated as mediators between neuroinflammation and neuronal dysfunction (e.g., decreased neurogenesis, synaptic plasticity and LTP), leading to cognitive impairment (Barrientos et al., 2004; Cortese et al., 2011; Yirmiya and Goshen, 2011).

Although POCD occurs most frequently in the elderly, it is also known to occur in younger adult patients (Monk et al, 2008). We have previously developed a rat model of POCD after abdominal surgery with mesenteric ischemia-reperfusion (Hovens et al., 2013). Healthy young adult rats coped well with the procedure, with no peri-operative deaths, minimal weight loss, and evidence of a robust inflammatory response to the procedure.

The aim of the current study was to investigate the time course of POCD and the involvement of (neuro)inflammation and changes in the BDNF pathway. We therefore used our existing model to assess aspects of learning and memory, exploratory behavior and markers of (neuro)inflammation, BDNF and neurogenesis at 1, 2 and 3 weeks following surgery in young adult rats.

2. Methods and materials

2.1. Design

Young adult rats were subjected to abdominal surgery and received a jugular vein catheter under anesthesia ($n = 36$). Learning, memory and exploratory behavior were assessed during postoperative week one (S1, $n = 12$), two (S2, $n = 12$), or three (S3, $n = 12$), followed by sacrifice on day 7, 14 or 21 after surgery, respectively (Fig 1). Naïve control animals (C, $n = 12$) underwent testing and sacrifice together with the three surgery groups (4 animals at each time point). Animals that only received anesthesia (A, $n = 12$) underwent testing and sacrifice together with S1.

As implantation of a jugular vein catheter is a surgical intervention in itself, in a control experiment the behavioral consequences of this procedure were studied during the second week following the intervention. Rats that only received a jugular vein catheter ($n = 10$) were compared with rats that remained naïve ($n = 10$).

All behavioral tests were conducted in a room adjacent to the housing room, under dim light conditions, in the first half of the dark phase.

2.2. Experimental animals

Three months old male Wistar rats (HsdCpb:WU, Harlan, Venray, NL) were individually housed in cages of $24 * 24 * 36$ cm in a room with a temperature of 20 ± 2 °C and humidity of $50 \pm 10\%$. Rats had ad libitum access to laboratory chow and tap water. The animals were kept on a 12:12 light:dark cycle (lights on at 9.00 a.m.). All experiments were approved by the local animal experiment and welfare committee (Dier Experimenten Commissie, Groningen, The Netherlands).

2.3. Surgery

Abdominal surgery was performed on rats ($n = 36$) as described before (Hovens et al., 2013). In short, under sevoflurane anesthesia (3% sevoflurane in O_2 at 0.7 L/min) and buprenorphine analgesia (0.003 mg/kg s.c.) the gastrointestinal tract was exteriorized and the upper mesenteric artery clamped for 30 min. Clamping of the upper mesenteric artery leads to a restriction of blood flow in the mesenteric vascular bed, although the presence of collateral arteries allows some perfusion (Petrat et al., 2010). We consider this abdominal surgery a model to mimic major abdominal surgery in humans (Grootjans et al., 2010a,b). The animals that received abdominal surgery were equipped with an indwelling jugular vein catheter during the abdominal surgery procedure, to allow timed blood sampling with minimal handling (Steffens, 1969). A group of rats that received only anesthesia and analgesia ($n = 12$) was kept under sevoflurane anesthesia for 1 h. Analgesia and blood sampling were performed in accordance with the surgery group.

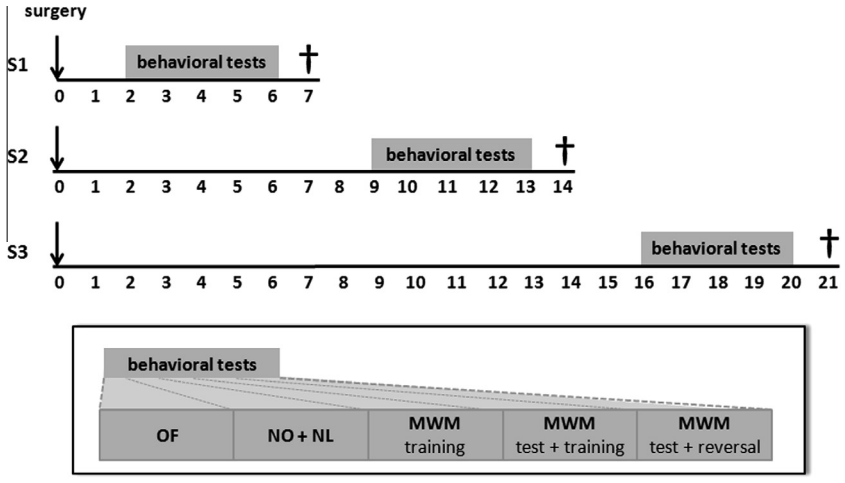

Fig. 1. Experimental design. For the experimental groups that underwent behavioral testing during week one (S1), two (S2) or three (S3) following surgery a time axis is shown displaying the number of days following surgery (↓). S1, S2 and S3 underwent a series of behavioral tests during a period of 5 days starting on day 2, 9 and 16, respectively. An inset shows the order the behavioral tests were performed. In this inset each block represents one day. The day after the last behavioral test the animals were sacrificed (†).

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