Exploring novel interventions for post-operative cognitive dysfunction in rat models
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DOI:
10.33612/diss.826261263

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Postoperative cognitive dysfunction (POCD)

Globally, life expectancy is rising due to improved living standards, health care, and nutrition. Moreover, medical technology and anaesthetic care have made surgeries safer for older patients, resulting in more elderly and otherwise vulnerable people undergoing surgery (Kotekar et al., 2018). However, this population tends to develop more complications after surgery than the younger patients. One of the complications after surgery, especially in these aged patients, includes cognitive decline (Rasmussen, 2006; van Harten et al., 2012). After surgery, patients can experience transient declines in short-term and long-term memory (delirium), which can reverse after a few days (POD) (Hovens et al., 2013, Kotekar et al., 2018). However, although the cognitive function of a part of the patients normalizes within a month after surgery, between 10 and 40%, of the patients, depending on the definition, experiences a more persistent or progressive state of cognitive impairment called postoperative cognitive dysfunction (POCD) (Evered et al., 2011; Hovens et al., 2013; Monk et al., 2008; Plas et al., 2017; Price et al., 2008). POCD was first investigated by Dr. Bedford in 1955, as he noticed that elderly patients were cognitively changed after surgery, displaying symptoms of dementia that could persist for months after the surgical procedure (BEDFORD, 1955). Since recognition, extensive progress has been made in the POCD research field. However, interpretation of results is hampered by the lack of a clear consensus on the definition of POCD. The clinical diagnosis of POCD requires the examination of different cognitive domains through specific and sensitive neuropsychological tests (Polunina et al., 2014). Because of the absence of a gold-standard definition for diagnosing POCD, often neuropsychological tests differ widely between studies and more or less stringent definitions of POCD are used (Bhamidipati et al., 2017; Glumac et al., 2018, 2019; Newman et al., 2007). This inconsistency presents a major obstacle in POCD research. Despite the difficulties in the assessment and definition of POCD, making today’s literature difficult to interpret, the consequences of POCD are clearly impacting patient’s daily life, as well as that of his/her caretakers. POCD is characterized by dementia-like symptoms such as memory impairment, problems in information processing, concentration and executive functions and memory (Hovens et al., 2012; Krenk et al., 2010). As these symptoms become more progressive, the risk for the development of other neurodegenerative disorders, such as Alzheimer’s disease (AD), increases as well (Hu et al., 2010; Vanderweyde et al., 2010). Moreover, the one-year mortality is almost twice as high for patients with POCD compared to those without POCD (Fodale et al., 2010; Leslie, 2017; Lin et al., 2020). Hence the occurrence of POCD is associated with reduced quality of life, increased dependency on social services, increased disability and mortality risk
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(Chen et al., 2014; Monk et al., 2008; Saczynski et al., 2012; Steinmetz et al., 2009; Vanderweyde et al., 2010). These problems can be a big burden not only for the patients but also for the families and health care systems (van Harten et al., 2012). The severe impact on a patient’s and their families and caretakers’ daily life stresses the need for therapy. However, so far, no therapy is available to either prevent or to treat POCD. A lack of understanding of the underlying mechanism hampers the development of effective therapeutic interventions.

Pathophysiology

In order to investigate mechanisms leading to POCD, many options were evaluated. Initially factors such as general anesthetics, formation of micro-emboli, surgery-induced hypoperfusion of the brain and peri-operative stress have been proposed as culprit for POCD. However, results remained inconclusive so far (Fontes et al., 2014; Gasparovic et al., 2013; Ji et al., 2013; Krenk et al., 2010; Rodriguez et al., 2005; Salazar et al., 2011). Nowadays, evidence suggest that there are multiple factors that can play a role in the development of POCD. Neuroinflammation (Luo et al., 2019), oxidative stress (Netto et al., 2018), mitochondrial dysfunction, neurotrophic support impairment (Fan et al., 2016), blood-brain barrier (BBB) (Zhang et al., 2016; Zhu et al., 2018), and synaptic damage (Xiao et al., 2018) have been proposed to play a role in POCD development. During the last decades, more studies focused on a derailed systemic inflammatory response, resulting from the local surgery-induced inflammatory response necessary for wound healing, as initiator for POCD. Indeed, accumulating evidence suggest that a derailed inflammatory response could be a key player in the development of POCD (Cibelli et al., 2010; Lin et al., 2020; Peng et al., 2013; Skvarc et al., 2018; Terrando et al., 2010; van Harten et al., 2012). Although local inflammation during and after surgery is needed for (wound) healing, and low levels of immune activation are necessary for regulation of normal cognitive functions, an exacerbated inflammatory response can affect cognitive processes and lead to POCD (Cibelli et al., 2010; Peng et al., 2013; Yirmiya & Goshen, 2011). During surgery, tissue is damaged, which causes releases of intracellular substances causing the immune system to be activated (Noll et al., 2017). Subsequently, the peripheral immune system will upregulate the expression of pro-inflammatory factors, such as IL-6 and TNF-α by macrophages (Li et al., 2018; Lin et al., 2020). Once released into the systemic circulation, these inflammatory factors can trigger the central response and induce neuroinflammation through the BBB or stimulation of the vagal afferent nerves (Dilger & Johnson, 2008; Galea et al., 2007; Ma et al., 2017; Maier, 2003). Some cytokines, such as TNF-α, IL-1β, and IL-6, can cross the BBB
passively or actively (Dilger & Johnson, 2008; Galea et al., 2007), other cytokines can bind to receptors on the endothelial cells of the BBB, resulting in the secretion of inflammatory factors in the central nerves system (CNS). When activated by immune factors in the periphery, the vagal afferent nerves can rapidly activate central inflammatory pathways (Dilger & Johnson, 2008; Maier, 2003). These processes can in turn stimulate the immune cells of the brain, microglia, as well as other immune cells, including bone marrow-derived macrophages (BMDMs), mast cells and T cells in the CNS to release more reactive oxygen species and other inflammatory factors. In the end this will result in aggravated neuroinflammation, which can lead to cognitive dysfunction, initiating POCD (Barrientos et al., 2012; Beloosesky et al., 2007; Bettcher et al., 2021; Cibelli et al., 2010; Dilger & Johnson, 2008; Peng et al., 2013; Wan et al., 2007; Wang et al., 2017; Yirmiya & Goshen, 2011; Zhu et al., 2018). Neuroinflammation can have a negative effect on neuronal processes either directly or indirectly. Directly it can act by activating apoptotic pathways or interfering with long term potentiation, and indirectly it can act through interactions with the neurotransmitter systems neurotrophins, or amyloid beta and tau processing (Andreotti et al., 2015; Forrest et al., 2003; Kline et al., 2012; Klinger et al., 2013; Price et al., 2014; Xie et al., 2013; Yirmiya & Goshen, 2011). Moreover, microglia also play a role in modulation of neuronal function by regulating pruning (elimination) of weaker synapses in both physiologic and pathologic processes (Geloso & D’Ambrosi, 2021).

Although these studies have indeed led to a better understanding of the pathophysiology of POCD, there are still gaps to bridge in the understanding of POCD development, and hence a rational for therapy. An appropriate animal model, expressing as many as possible aspects of POCD, would help to unravel the pathophysiology and study potential treatment.

**Animal models**

In 2014 Hovens et al developed a rat model for this POCD, enabling us to investigate the pathophysiology and subsequently investigate therapeutically interventions for POCD in animals (Hovens et al., 2014). The model was developed to mimic the surgical procedures in the clinic and was discussed in detail with one of the surgeons in the hospital. It resulted in major abdominal surgery with mesenteric ischemia-reperfusion. Results regarding behavioral evaluation and brain analysis in young healthy rats showed great similarity to the clinical symptoms. Moreover, they demonstrate that the surgery-induced local inflammatory response could result in increased circulating (pro)inflammatory markers, reflected in the brain as
neuroinflammation, associated with cognitive dysfunction (Hovens et al., 2014). This is in agreement with results from other labs (Barrientos et al., 2006; Dilger & Johnson, 2008; Hudetz et al., 2011; Su et al., 2013). Even though these studies provided consistent and relevant data for POCD research, young and healthy rats may not offer the best representation of the patients developing POCD, as they do not express the main risk factors for POCD, such as aging and worse pre-operative health, including hypertension, uremia, hyperglycemia and liver disease (Kapoor et al., 2019; Kotekar et al., 2018; Rundshagen, 2014; Sauër et al., 2009). Accordingly, Hovens et al also studied POCD development after abdominal surgery in aged rats and rats with worse pre-operative health. Indeed, they showed that worse pre-operative health and advanced age was reflected in more wide-spread cognitive decline and exaggerated neuroinflammation (Hovens et al., 2013; Hovens et al., 2015a, 2015b). However, these risk factors were superimposed on otherwise healthy animals, stressing the notion for a clinically more relevant model representing the elderly and vulnerable patient population at risk for POCD. As age is the main risk factor for POCD, a logical step would be to study the development of POCD and potential therapeutical interventions in aged rats. However, aged rats obtained from commercial breeders may not optimally reflect the older human population, as they are bred under optimal conditions, including optimal food, pathogen free conditions, climatized rooms and socialization restricted to their own sex. These conditions are not representative for the conditions of the aged human population. Therefore, alternative models are worthwhile to explore for studying the effects of POCD and potential treatment. In this regard, the Zucker rat could provide a clinically relevant increased-risk model, as it simultaneously displays many risk factors for worse post-surgical outcome, including obesity, hyperglycemia kidney dysfunction and hypertension (Aleixandre de Artiñana & Miguel Castro, 2009). Moreover, from a relatively young age (±6 months) these metabolic syndrome-like rats display low-grade inflammation, cognitive dysfunction and neuroinflammation (Aleixandre de Artiñana & Miguel Castro, 2009). Together, these factors may have predictive value for impaired recovery and POCD in patients, making these Zucker rats potentially a good representative model for the vulnerable and older patient population undergoing surgery.
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Therapy

As of today, there is no effective treatment for POCD available in the clinic. As increasingly more older patients will undergo surgery the upcoming years, it is to be expected that POCD incidences will also increase. Therefore, there is a high need for effective therapeutic interventions to prevent or treat POCD. According to the inflammation hypothesis, a general anti-inflammatory approach that could interfere with the inflammation in the whole body could be effective as POCD treatment. One of the most generally used anti-inflammatory drug is ibuprofen. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used to treat mild to moderate pain, and helps to relieve symptoms of arthritis, including inflammation and swelling (Busson, 1986; Kantor, 1979; Rainsford, 2009). Based on the general anti-inflammatory properties of ibuprofen, it could be effective in prevention or alleviation of POCD symptoms. This approach would be supported by other studies that tested anti-inflammatory interventions, that seemed to be beneficial in prevention of POCD in experimental (Barrientos et al., 2012; Hu et al., 2018; Jiang et al., 2015; Kamer et al., 2012) and clinical studies (Valentin et al., 2016; Zhu et al., 2016). However, none of these interventions have reached the clinical practice so far. Other studies confirmed that inhibition of peripheral inflammation alone may not be sufficient enough to recover cognitive impairment in POCD (Mohammadian et al., 2019). Hence it is likely that other factors also play an role in the development of POCD. Therefore, other treatments that combine anti-inflammatory effect with cognition-improving aspects, are worthwhile to explore on their potential for successful treatment for POCD. J147 could provide a promising new therapeutic avenue in this regard, as it combines anti-inflammatory properties with neuroprotective properties. It has already been shown to be effective in most common age-associated neuropathy models (Currais et al., 2015; Daugherty et al., 2018; Goldberg et al., 2020; Goldberg et al., 2018; Prior et al., 2016). Although J147 initially was developed as anti-Alzheimer’s disease compound, it has also been proven to be effective as anti-depression (Li et al., 2020; Lian et al., 2018; Pan et al., 2021), general anti-dementia (Goldberg et al., 2018; Prior et al., 2013) and anti-diabetic drug (Daugherty et al., 2018). In addition, it has been associated with improvement of synaptic function, cognitive performance, reduction of inflammatory and oxidative stress markers and prevention of BBB leakage (Currais et al., 2015; Daugherty et al., 2018; Emmanuel et al., 2019; Goldberg et al., 2018; Larrick & Mendelsohn, 2018; Prior et al., 2013; Prior et al., 2016). Moreover, J147 is a high affinity molecular target for α-subunit of ATP synthase (ATP5A) in the mitochondria and thereby able to regulate variety of metabolic signaling in the cell (Goldberg et al., 2018; Neupane et al., 2019). As J147 has proven its effectiveness in
neuroprotection in age-associated toxicities it is currently tested in Phase I clinical trials (NCT03838185).

**Aim and outline of this thesis**

Although substantial progress has been made in understanding the mechanism underlying POCD, the pathophysiology of POCD still remains not fully elucidated. Moreover, steps have been made towards effective treatment for POCD, however none have made it into the clinic so far. Therefore, the aim of this thesis is to elucidate on the mechanism of POCD and explore novel interventions for POCD in different rat models.

Firstly, in **chapter 2** the effects of treatment with a general anti-inflammatory drug, ibuprofen, are studied in healthy young as well as aged rats. As besides inflammation, other factors can play a role in development of POCD, a new drug, named J147, combining amongst others, anti-inflammatory and general anti-ageing and anti-dementia properties, could be effective in prevention of POCD. Therefore, in **chapter 3**, effects of J147 are tested in a young healthy rat model for POCD. Since it would further increase clinically relevance to study J147 in an increased-risk model, better mimicking the patient group that develops POCD. Zucker rats display many risk factors associated with development of POCD in patients. Therefore, **chapter 4** explores the effects of J147 on early post-operative recovery in a Zucker rat model, and subsequently in **chapter 5** we investigate the effect of J147 on late post-operative recovery, including POCD, in Zucker rats. Finally, in **chapter 6** the general discussion gives an overview of the outcomes of this thesis, puts the data in perspective of the current literature, and provides future outlooks.
Chapter 1

References


Chapter 1


