Pathophysiological and behavioral effects of systemic inflammation in aged and diseased rodents with relevance to delirium

Schreuder, Leroy; Eggen, Bart J; Biber, Knut; Schoemaker, Regien G.; Laman, Jon D; Rooij, de, Sophia E.

Published in:
Brain, Behavior, and Immunity

DOI:
10.1016/j.bbi.2017.01.010

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

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

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Review Article
Pathophysiological and behavioral effects of systemic inflammation in aged and diseased rodents with relevance to delirium: A systematic review
Leroy Schreuder,⇑, B.J. Eggen, Knut Biber, Regien G. Schoemaker, Jon D. Laman, Sophia E. de Rooij

A R T I C L E  I N F O
Article history:
Received 28 July 2016
Received in revised form 26 December 2016
Accepted 10 January 2017
Available online 11 January 2017

Keywords:
Acute cognitive dysfunction
Sickness behavior
Aging
Neuroinflammation
Microglia
Astrocytes
Cytokines
IL-6
Surgery
Infection

A B S T R A C T
Delirium is a frequent outcome for aged and demented patients that suffer a systemic inflammatory insult. Animal models that reconstruct these etiological processes have potential to provide a better understanding of the pathophysiology of delirium. Therefore, we systematically reviewed animal studies in which systemic inflammation was superimposed on aged or diseased animal models. In total, 77 studies were identified. Aged animals were challenged with a bacterial endotoxin in 29 studies, 25 studies superimposed surgery on aged animals, and in 6 studies a bacterial infection, Escherichia coli (E. coli), was used. Diseased animals were challenged with a bacterial endotoxin in 15 studies, two studies examined effects of the cytokine IL-1β, and one study used polyinosinic:polycytidilic acid (poly I:C). This systematic review analyzed the impact of systemic inflammation on the production of inflammatory and neurotoxic mediators in peripheral blood, cerebrospinal fluid (CSF), and on the central nervous system (CNS). Moreover, concomitant behavioral and cognitive symptoms were also evaluated. Finally, outcomes of behavioral and cognitive tests from animal studies were compared to features and symptoms present in delirious patients.

© 2017 Elsevier Inc. All rights reserved.
1. Introduction

Delirium is a common and severe neuropsychiatric syndrome predominantly characterized by acute and temporary disturbances in attention fluctuating over time. Other associated symptoms include disorganized thinking, altered arousal, perceptual and cognitive disturbances, and disruption of the sleep-wake cycle (Inouye et al., 2014; Macullich et al., 2013). In 1959, Engel and Romano were the first to demonstrate a close association between clinical symptoms of delirium and a generalized slowing of the electroencephalogram (Engel and Romano, 2004). Other milestones on delirium diagnostics along with critical milestones on the level of classification, laboratory and imaging diagnostics, preventive and therapeutic opportunities and animal disease models are illustrated in Fig. 1.

It has become clear that aging and dementia are strong predisposing risk factors for delirium, and that systemic inflammation is an important trigger (Maclullich et al., 2008). So far, the pathophysiological relationship of this and how these factors interact to produce delirium is poorly understood. Not only the pathogenesis of delirium, but also its symptoms and subtypes and the pathophysiological mechanisms for the accelerated progression of cognitive decline and dementia after delirium are still unexplained (Wiltin et al., 2010; Feng et al., 2009).

Preclinical animal models that superimpose systemic inflammation on a background of aging or dementia have potential to be extremely useful for testing mechanistic hypotheses about delirium pathophysiology, long term effects on progression of underlying disease, and to examine responsiveness to pharmacological interventions. With this in mind, we have systematically reviewed preclinical animal studies in which systemic inflammation was superimposed on animal models of aging or various animal models of neurodegenerative disease. We will present a comprehensive overview of altered mechanistic processes and changes in behavior and cognition in animals with an increased vulnerability (i.e. aged or diseased animals) to systemic inflammation. In addition to systemic inflammation delirium has other precipitating factors, but discussion of these are beyond the scope of this review.

As we hypothesize that not a single animal model can recapitulate the full symptomatology of delirium, this systematic review discusses both values and limitations of animal models by comparing how they relate to pathophysiological changes and neuropsychological symptoms present in delirious patients. Finally, we attempt to provide suggestions and opportunities for future preclinical and clinical research into delirium pathophysiology.

2. Methods

2.1. Search strategy


2.2. Selection criteria

Studies were included if they met the following inclusion criteria: 1) study must be performed on animals; 2) animals must be challenged with systemic inflammation of any origin; 3) included animals must be at least 16 months of age to be considered aged or suffer from an underlying neurodegenerative disease or...
progeroid syndrome, accelerating the aging process; 4) CNS inflammatory, serum, plasma, or cerebrospinal fluid (CSF) levels and/or behavioral/cognitive impairments must be examined; and 5) the study must be an original full paper which presents unique data. Inclusion criterion 4 allows that studies that pay no attention to delirium or cognitive function are included. These studies are useful and may provide insight into the pathophysiology of delirium, because systemic inflammation is superimposed on high risk animals and combination of these elements is a frequent route to delirium. Exclusion criteria were set up for the preparation of a structured flowchart of the study selection phases. Exclusion criteria are: 1) study is conducted at the cellular level, i.e. cells are extracted from the animal and stimulated ex vivo; 2) any manipulation directly in or around the brain not representative for a neurodegenerative disease or biological mechanism of aging; 3) only adult animals up to 6 months of age are examined; 4) animals receive a intracerebroventricular lipopolysaccharide (LPS) injection; and 5) a focus solely on other organs than the brain (e.g. liver, kidney, lung or heart). Two researchers were in charge of data extraction. One researcher extracted data, and when in doubt the second researcher was consulted. Further, extracted data of studies were discussed during group meetings with all researchers and any differences were resolved by discussion.

### 2.3. Data extraction

The following parameters were extracted from the studies: inflammatory alterations in serum or plasma, CSF and brain tissue, alterations in brain resident glial cells, and concomitant behavioral and cognitive changes. In addition, other key determinants that were extracted include dose, type and site of the bacterial endotoxin, bacterial infection, poly I:C, and cytokine, and the type of surgical intervention. Furthermore, age, genetic background, type of underlying disease and the examined time period after systemic inflammatory challenge were extracted.

#### 2.4. Methods for the valuation of animal models

To determine the overall value of the rodent models representing symptoms of delirium, we utilize a general framework that is used to assess the validity of rodent models. It consists of five general criteria: homological validity, pathogenic validity, mechanistic validity, face validity and predictive validity. These precisely defined criteria have been proposed by Belzung and Lemoine (Belzung and Lemoine, 2011). The first criterion, homological validity, can be subdivided into two categories, species validity, which considers whether a certain species, in this case rats or mice, is favorable to model the syndrome of delirium, and strain validity, which examines what strain would be the most relevant choice for modeling delirium. The second criterion, pathogenic validity evaluates the similarities of the processes between humans and rodents that induce the disease. Triggering validity, a subcategory of pathogenetic validity, assesses the similarities of triggering factors that ultimately produce the disease. We will redefine the concept of ontopathogenic validity, because early environmental factors have not yet been determined to play a role in the onset of delirium. It is prior pathology or aging that makes individuals more prone to develop delirium. For purposes of this systematic review, ontopathogenic validity will be defined as intrinsic factors such as prior pathology or aging, that render the organism more vulnerable to triggering factors. The third criterion, mechanistic validity, refers to the shared similarities of the underlying biological mechanism that is assumed to result in delirium. In addition, mechanistic validity refers to the mechanism that produces the symptoms
and biological markers of delirium. The fourth criterion is face validity. It consists of ethological validity and biomarker validity. The former evaluates the similarity of behaviors, whereas the latter refers to the shared similarities of biological markers within the organisms. The fifth and final criterion is termed predictive validity. Predictive validity can be partitioned into induction validity and remission validity. Induction validity examines the similarities of the relation between triggering factors and the occurrence of disease. Remission validity considers the similarities of observable treatment outcomes between the rodent model and delirium in humans. In summary, an optimal rodent model for delirium requires a species or strain that is favorable to model delirium, displays an analogy of triggering factors, intrinsic factors, underlying biological mechanisms, behavioral symptoms and biological markers. Moreover, there has to be a relationship between triggering factors and occurrence of disease, and similarities between observable treatment outcomes should be existent.

### 3. Results

Our systematic search included a total of 3006 articles and 158 were selected for further review (Fig. 2). In total, 75 studies met inclusion criteria and 2 articles were selected from reference lists. Thus, 77 studies were included in this review. Rats and mice were the only animal models retrieved by our systematic search. Therefore, we adopt the term rodent models instead of animal models. Four different etiological groups have been constructed to examine the effect of distinct precipitating factors that are superimposed upon differential predisposing factors. These groups are 1) bacterial endotoxin superimposed upon aging, 2) bacterial infection superimposed upon aging, 3) a surgical procedure superimposed upon aging, and 4) bacterial endotoxin, poly I:C or a cytokine superimposed upon preexisting neurodegenerative disease or progeroid syndrome. The latter focuses on the interaction between systemic inflammation and preexisting neurodegenerative disease.

![Structured flow chart on the study selection process](image)
or progeroid syndrome, whereas the former focuses on the interaction between systemic inflammation and aging. Our systematic search did not retrieve rodent models where either a live infectious agent or a surgical intervention was superimposed upon neurodegenerative disease or progeroid syndrome. The aforementioned groups are referred to as Aged x Bacterial endotoxin, Aged x Bacterial infection, Aged x Surgery and Diseased x Bacterial endotoxin/poly I:C/cytokine.

3.1. Aged x bacterial endotoxin

3.1.1. Description of studies

The effects of a single dose of bacterial endotoxin on systemic and central inflammation and behavior of aged rodents were evaluated in 29/77 studies (Table 1a). Different types of bolus LPS including E. coli and Pseudomonas aeruginosa were used to mimic a bacterial infection. None of the studies evaluated multiple doses of LPS over time. The majority of the included studies injected 0.33 mg/kg LPS intraperitoneally (i.p.). This dosage was chosen because it induces a mild transient sickness behavior in adult rodents. Several other studies i.p. injected LPS doses varying between 1 mg/kg up to 4 mg/kg (Kawano et al., 2015; Alvarez-Lopez et al., 2014; Donoso et al., 2008; Tateda et al., 1996), with the latter concentration resembling relatively severe sepsis. One study employed intravenous (i.v.) administration of LPS (Vasconcelos et al., 2015). Further, one study challenged mice with an acute or repeated i.p. administration of 0.2 mg/kg staphylococcal enterotoxin A (SEA) (Kohman et al., 2009). In total, 24/29 studies focused on mice, whereas, 5/29 studies examined rats. Furthermore, 24/29 studies employed adult counterparts as controls and 5/29 studies only evaluated aged rodents.

3.1.2. Circulating inflammatory cytokines

Activated peripheral innate immune cells secrete inflammatory cytokines that signal to the brain via blood borne as well as neural routes (Perry et al., 2007). In total, 11/29 studies evaluated whether there were any age-dependent effects of systemic inflammation, induced by LPS, on systemic cytokine levels (Table 1a). A number of studies showed that systemic cytokine levels of IL-6, TNF-α, IL-10 were increased in aged rodents with respect to adult counterparts between 2 and 24 h post-LPS challenge (Campbell et al., 2014; Burton and Johnson, 2012; Mouton et al., 2012; Henry et al., 2009; Godbout et al., 2008, 2005; Donoso et al., 2008; Tateda et al., 1996). Not only the secretion of cytokines differed between aged and adult rodents, but also the expression of cytokine receptors in the brain after LPS challenge (Utsuyama and Hirokawa, 2002). One study assessed whether this increased CNS inflammatory response was associated with changes in neuron morphology and demonstrated increased neuronal hippocampal atrophy in aged rodents challenged with LPS (0.33 mg/kg) (Richwine et al., 2008). Increased levels of neuroinflammation observed in the aged may be partially explained by the concept of microglial priming. When microglia are primed they are hyper-responsive to systemic inflammatory signals. In this hyper-responsive state exaggerated amounts of proinflammatory cytokines are produced and these can impair neuronal function and promote neurodegeneration, ultimately leading to behavioral and cognitive dysfunction. This concept of microglial priming was first demonstrated in the ME7 model of prion disease (Cunningham et al., 2005; Combrinck et al., 2002). Now microglial priming has also been observed in aging models. Aged rodents showed an increased number of microglia that stained for tomato lectin with respect to adult rodents (Chen et al., 2008). Isolated microglia from aged rodents had an increased expression of major histocompatibility complex (MHC)-II, a marker of activated microglia (Burton and Johnson, 2012; Henry et al., 2009; Richwine et al., 2008; Godbout et al., 2005). Moreover, isolated microglia also demonstrated increased transcript levels of Toll-like receptor 2 (TLR2), IL-1β, IL-6, TNF-α, IL-10, IDO and inducible nitric oxide synthase (iNOS) post-LPS challenge (0.33 mg/kg) and this effect was more pronounced in the aged (Fenn et al., 2012; Henry et al., 2009). Increased astrocyte activation was observed in aged rodents challenged with LPS, suggesting that astrocytes, and not only microglia, may also play an important role in the aged brain, as (Fu et al., 2014).

3.1.4. Behavior and cognition

Age-related increases in CNS inflammation are associated with behavioral and cognitive deficits. In total, 15/29 studies examined the association between age-related increases in CNS inflammation and behavioral and cognitive outcomes after a single dose of LPS or SEA (Table 1a). It is known that systemic inflammation induces lethargy, reduced locomotion, anhedonia and reduced appetite. Conjointly this cluster of changes is termed sickness behavior and in health these responses are adaptive (Dantzer, 2004). However, exaggerated CNS inflammation in aged rodents is associated with exaggerated sickness behavior. Aged rodents challenged with LPS (0.33 mg/kg) showed a greater and prolonged suppression of locomotor function and social exploratory behavior compared to adult rodents challenged similarly (Townsend et al., 2014; Burton et al., 2013; Martin et al., 2013; Wynne et al., 2010; Abraham and Johnson, 2009a; Berg et al., 2005; Godbout et al., 2005). Pretreatment with IL-1RA attenuated LPS-induced sickness behavior and CNS IL-1β transcript levels. These findings suggest that central IL-1β is responsible for the exaggerated sickness behavior observed in aged rodents after LPS challenge. Acute administration of SEA resulted in prolonged hyponeophagia (decreased consumption of a novel food) in aged rodents relative to adult rodents (Kohman et al., 2009). One study showed exaggerated and prolonged depressive-like behavior in aged rodents challenged with LPS (0.33 mg/kg), lasting up to 72 h after the systemic insult (Godbout et al., 2008). Inflammatory stimuli can also have deleterious effects on cognitive processing. LPS injection (0.33 mg/kg) produced acute impairments of working memory in aged rodents compared to adults. LPS-induced systemic inflammation interfered with their ability to effectively integrate the altered location of the platform in the 5-arm radial water maze test. This was associated with an exaggerated CNS IL-1β, IL-6 and TNF-α response (Chen et al., 2008). In the two-way active avoidance test LPS-induced
### Table 1a

Aged × bacterial endotoxin (E. coli, P. aeruginosa, and SEA).

<table>
<thead>
<tr>
<th>Study</th>
<th>Genetic background</th>
<th>Age (months)</th>
<th>Type/dose/site of LPS/SEA (mg/kg)</th>
<th>Time points (h)</th>
<th>Serum</th>
<th>Sickness behavior and cognitive deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2008</td>
<td>BALB/c</td>
<td>3–6 m 22–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4</td>
<td>IL-1β, TNF-α, IL-6 transcript, microglial activation (number)</td>
<td>Performance on 5-arm radial water maze test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IL-1β transcript, #reveratrol ↓ IL-1β</td>
<td>Performance on morris water maze reversal test, #reveratrol, performance, locomotor activity</td>
</tr>
<tr>
<td>Abraham 2009b</td>
<td>BALB/c</td>
<td>3–6 m 22–24 m</td>
<td>E. coli i.p. (0.04)</td>
<td>4, 24</td>
<td>IL-6</td>
<td>Performance on fear conditioning test, #sgp130, performance</td>
</tr>
<tr>
<td>Burton 2012</td>
<td>BALB/c</td>
<td>3–6 m 22–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>1,2,4,6,8,48</td>
<td>IL-6</td>
<td>Performance on two-way active avoidance test, Performance on attentional set-shifting test</td>
</tr>
<tr>
<td>Tarr 2011</td>
<td>CS78/6 J (rat)</td>
<td>4 m 18 m</td>
<td>E. coli i.p. (0.25)</td>
<td>1–6 d</td>
<td>IL-1β, TNF-α, IL-6 transcript, #resveratrol; IL-1β activation (number)</td>
<td>Performance on morris water maze reversal test, #resveratrol, performance, locomotor activity</td>
</tr>
<tr>
<td>Culley 2014</td>
<td>Fisher 344</td>
<td>24 m</td>
<td>N/A i.p. (0.05)</td>
<td>2,24,48,72</td>
<td>TNF-α, CCL2, IL-1β</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Kawano 2014</td>
<td>Wistar (rat)</td>
<td>25 m</td>
<td>N/A i.p. (5)</td>
<td>7 d</td>
<td>IL-1β, TNF-α, #CNS inflammation</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Godbout 2008</td>
<td>BALB/c</td>
<td>3–6 m 20–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4,24,48,72</td>
<td>IL-1β, TNF-α, #resveratrol; IL-1β activation (number)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Kohman 2009</td>
<td>CS78/6 J</td>
<td>4 m 20 m</td>
<td>E. coli i.p. (0.33)</td>
<td>2,4,6,24</td>
<td>IL-1β, IL-6, IL-6 transcript, protein, microglial activation (MHC-II)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Godbout 2009</td>
<td>BALB/c</td>
<td>3–6 m 22–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>2,4,8,24</td>
<td>IL-1β, IL-6, microglial activation (MHC-II)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Townsend 2014</td>
<td>BALB/c</td>
<td>4 m 18 m</td>
<td>E. coli i.p. (0.33)</td>
<td>2,4,8,24</td>
<td>IL-1β, IL-6, IL-6 transcript, protein, microglial activation (MHC-II)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Wynne 2010</td>
<td>BALB/c</td>
<td>3–6 m 18–22 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4,8,24</td>
<td>IL-1β, IL-6, IL-6 transcript, microglial activation (MHC-II)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Berg 2005</td>
<td>BALB/c</td>
<td>18 m</td>
<td>E. coli i.p. (0.33)</td>
<td>2,4,8,24</td>
<td>IL-1β, IL-6, IL-6 transcript, #resveratrol; IL-1β activation (number)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Martin 2013</td>
<td>CS78/6 J</td>
<td>22 m</td>
<td>E. coli i.p. (0.33)</td>
<td>24</td>
<td>IL-1β, TNF-α, IL-10 transcript, #microglial activation (MHC-II)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Burton 2013</td>
<td>BALB/c</td>
<td>3–6 m 20–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4,6,8,24</td>
<td>IL-1β, IL-6, IL-6 transcript, microglial activation (MHC-II)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Abraham 2009a</td>
<td>BALB/c</td>
<td>3–6 m 22–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>2,4,8,24</td>
<td>IL-1β, IL-10, #IL-1RA, IL-1β</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Henry 2008</td>
<td>BALB/c</td>
<td>3–4 m 20–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4</td>
<td>IL-1β, IDO, TLR-2 transcript #minocycline; CNS inflammation</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Henry 2009</td>
<td>BALB/c</td>
<td>3–4 m 18–20 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4,8</td>
<td>IL-1β, IL-10, IL-6 transcript, #microglial activation (MHC-II)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Martin 2014</td>
<td>CS78/6 J</td>
<td>4 m 22 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4,24</td>
<td>IL-1β, TNF-α, IL-6, IDO transcript, #VWR no effect</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Fenn 2012</td>
<td>BALB/c</td>
<td>3–4 m 18–22 m</td>
<td>E. coli i.p. (0.33)</td>
<td>4,24</td>
<td>Microglia show no increase in IL-4Rα in response to LPS</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Donoso 2009</td>
<td>Fisher 344</td>
<td>6 m 15 m</td>
<td>P. aeruginosa i.p. (2)</td>
<td>1,2,4,6,12</td>
<td>TNF-α, IL-10</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Richwine 2008</td>
<td>BALB/c</td>
<td>6 m 22–24 m</td>
<td>E. coli i.p. (0.33)</td>
<td>3–6 m 22–24 m</td>
<td>Microglia show no increase in IL-4Rα in response to LPS</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Gomez 2006</td>
<td>BALB/c</td>
<td>2–3 m 18–20 m</td>
<td>P. aeruginosa i.p. (0.06)</td>
<td>24</td>
<td>IL-6</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Nolan 2002</td>
<td>Wistar</td>
<td>4 m 22 m</td>
<td>P. aeruginosa i.p. (0.1)</td>
<td>3</td>
<td>IL-1β, TNF-α, IL-6, IDO transcript, #VWR no effect</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Terao 2002</td>
<td>CS78/6 J</td>
<td>3 m 24 m</td>
<td>P. aeruginosa i.p. (0.06)</td>
<td>3</td>
<td>IL-1β, TNF-α, MCP-1 transcript</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Mouton 2012</td>
<td>CS78/6 J</td>
<td>6 m 22 m</td>
<td>E. coli i.p. (0.33)</td>
<td>2</td>
<td>IL-1β, TNF-α, MCP-1 transcript</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Utsuyama 2002</td>
<td>CS78/6 J</td>
<td>3 m 24 m</td>
<td>N/A i.p. (1)</td>
<td>1,2,4,6,24</td>
<td>Differential expression of receptors between young and aged (transcript)</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Tateda 1996</td>
<td>ICR</td>
<td>2 m 24 m</td>
<td>E. coli i.p. (4)</td>
<td>1,3,6,12</td>
<td>IL-1β, IL-6, TNF-α, IL-10</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Fu 2014</td>
<td>Wistar</td>
<td>20 m</td>
<td>E. coli i.p. (2)</td>
<td>1,3,7,30 d</td>
<td>TNF-α, IL-1β, NF-kB transcript, protein, astrogliosis</td>
<td>Performance on social exploratory test</td>
</tr>
<tr>
<td>Campbell 2014</td>
<td>CB6F1</td>
<td>4 m 26 m</td>
<td>E. coli i.p. (1)</td>
<td>3</td>
<td>TNF-α</td>
<td>Performance on social exploratory test</td>
</tr>
</tbody>
</table>

Overview of differential changes in aged rodents relative to adult controls when challenged with a bacterial endotoxin. Only changes in aged rodents are described. Genetic background, age of rodents, type, dose and site of the causative agents that induce systemic inflammation, and studied time points of each study are noted. Outcomes of studies are described as changes at the level of serum, CSF, CNS and behavior and cognition. Abbreviations: (*) only aged rodents were examined; (#) treatments were examined, (i.p.) intraperitoneal, (d) days. (N/A) not available.
In total, 15/17 studies examined the effects of an inflammatory challenge on inflammatory mediators in the CNS and 3/16 studies evaluated the effects of multiple inflammatory challenges on neuroinflammatory mediators (Table 1b). Microglia of ME7 mice are primed by chronic neurodegeneration, as evidenced by an increased number of microglia and morphological features of activation including attenuated ramification and an increased cell volume (Cunningham et al., 2005). At the functional level, LPS challenge (0.1 mg/kg) provoked an increased and prolonged transcription of CNS inflammatory mediators of the major proinflammatory cytokines IL-1β, TNF-α, IFN-γ, and IL-6 in ME7 mice compared to controls similarly challenged (Murray et al., 2012; Cunningham et al., 2009; Combrinck et al., 2002). Altered expression levels of other inflammatory mediators in response to LPS examined by these studies can be found in Table 1b. This systemic challenge also increased neuroapoptosis in ME-7 mice (Murray et al., 2011). Exacerbation of the CNS inflammatory response and increased neuroapoptosis has also been demonstrated in ME7 mice challenged with poly I:C, a TLR-3 agonist mimicking systemic viral infection (Field et al., 2010). A similar primed state of microglia induced by degenerative changes and an amplified cytokine response to LPS (1 mg/kg) was found in the CNS of Ercc1<sup>−/−</sup> mice when compared to controls. In addition, LPS-treated microglia of Ercc1<sup>−/−</sup> mice displayed increased phagocytosis (Raj et al., 2014). SAMP8 mice, another model of accelerated aging, did not mount an increased CNS inflammatory response after LPS (0.2 mg/kg) treatment with respect to their controls (Tha et al., 2000). An increased CNS cytokine response was also observed in a transgenic model of AD, Tg2576, challenged with LPS i.v. (1 mg/kg) relative to controls (Sly et al., 2001). Two other AD models including APPsw Tg and 3×Tg that received chronic LPS treatment for several weeks have demonstrated exacerbation of existing neuropathology as a consequence of increased neuroinflammation (Joshi et al., 2014; Kitazawa et al., 2005; Sheng et al., 2003). These exacerbations of existing neurodegeneration were also found in a rodent model for PD that received a single dose of IL-1β i.v. (Pott Godoy et al., 2008).

3.2.4. Behavior and cognition

Behavioral and cognitive consequences in diseased rodents after a systemic inflammatory challenge were evaluated in 9/17 studies (Table 1b). Increased CNS inflammatory responses in ME7 mice were found to be paralleled by exaggerated sickness behavior responses. ME7 mice showed a protracted decrease in locomotor activity and an increased hypothermic response after LPS challenge (0.4 mg/kg) compared to controls (Combrinck et al., 2002). Acute effects of LPS on motor coordination and muscle strength were also observed, and these were greater in ME7 mice than controls. ME7 mice recovered normal function after LPS, but at a later stage.

A full time-course analysis demonstrated that levels of major inflammatory mediators (IL-1β, IL-6, TNF-α) in plasma were increased to a similar extent in ME7 and control mice receiving an analogous challenge (0.1 mg/kg LPS) (Murray et al., 2012, 2011). Similar findings were obtained when poly I:C was used to induce systemic inflammation (Field et al., 2010). SAMP8 mice showed increased plasma IL-6 levels with respect to controls after LPS-challenge (2.9 mg/kg). However, these LPS doses were relatively high and would be more comparable with severe sepsis than mild to moderate infection (Alvarez-Lopez et al., 2014). Noteworthy, a large number of studies on ME7 mice come from a single lab, and have not been reproduced by others. This is an important point to consider, because reproducibility of animal inflammation models is a major issue, and is extensively reviewed elsewhere (Laman et al., 2017).

3.2.3. CNS inflammation

In total, 15/17 studies examined the effects of an inflammatory challenge on inflammatory mediators in the CNS and 3/16 studies evaluated the effects of multiple inflammatory challenges on neuroinflammatory mediators (Table 1b). Microglia of ME7 mice are primed by chronic neurodegeneration, as evidenced by an increased number of microglia and morphological features of activation including attenuated ramification and an increased cell volume (Cunningham et al., 2005). At the functional level, LPS challenge (0.1 mg/kg) provoked an increased and prolonged transcription of CNS inflammatory mediators of the major proinflammatory cytokines IL-1β, TNF-α, IFN-γ, and IL-6 in ME7 mice compared to controls similarly challenged (Murray et al., 2012; Cunningham et al., 2009; Combrinck et al., 2002). Altered expression levels of other inflammatory mediators in response to LPS examined by these studies can be found in Table 1b. This systemic challenge also increased neuroapoptosis in ME-7 mice (Murray et al., 2011). Exacerbation of the CNS inflammatory response and increased neuroapoptosis has also been demonstrated in ME7 mice challenged with poly I:C, a TLR-3 agonist mimicking systemic viral infection (Field et al., 2010). A similar primed state of microglia induced by degenerative changes and an amplified cytokine response to LPS (1 mg/kg) was found in the CNS of Ercc1<sup>−/−</sup> mice when compared to controls. In addition, LPS-treated microglia of Ercc1<sup>−/−</sup> mice displayed increased phagocytosis (Raj et al., 2014). SAMP8 mice, another model of accelerated aging, did not mount an increased CNS inflammatory response after LPS (0.2 mg/kg) treatment with respect to their controls (Tha et al., 2000). An increased CNS cytokine response was also observed in a transgenic model of AD, Tg2576, challenged with LPS i.v. (1 mg/kg) relative to controls (Sly et al., 2001). Two other AD models including APPsw Tg and 3×Tg that received chronic LPS treatment for several weeks have demonstrated exacerbation of existing neuropathology as a consequence of increased neuroinflammation (Joshi et al., 2014; Kitazawa et al., 2005; Sheng et al., 2003). These exacerbations of existing neurodegeneration were also found in a rodent model for PD that received a single dose of IL-1β i.v. (Pott Godoy et al., 2008).

3.2.4. Behavior and cognition

Behavioral and cognitive consequences in diseased rodents after a systemic inflammatory challenge were evaluated in 9/17 studies (Table 1b). Increased CNS inflammatory responses in ME7 mice were found to be paralleled by exaggerated sickness behavior responses. ME7 mice showed a protracted decrease in locomotor activity and an increased hypothermic response after LPS challenge (0.4 mg/kg) compared to controls (Combrinck et al., 2002). Acute effects of LPS on motor coordination and muscle strength were also observed, and these were greater in ME7 mice than controls. ME7 mice recovered normal function after LPS, but at a later stage.
Table 1b
Diseased × bacterial endotoxin, poly I:C, or IL-1β (Escherichia coli and Salmonella equine abortus).

<table>
<thead>
<tr>
<th>Study</th>
<th>Background/disease type</th>
<th>Type/dose/site of LPS, IL-1β or poly I:C (mg/kg)</th>
<th>Time points (hours)</th>
<th>Serum</th>
<th>CNS (inflammatory mediators and microglial activation)</th>
<th>Behavioral and cognitive deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham 2009</td>
<td>C57BL/6-ME7 Salmonella i.p. (0.1)</td>
<td>0–48, 6 w</td>
<td>IL-1β, TNF-α, IFN-β transcript; microglial activation (number + LPS-induced IL-1β production)</td>
<td>Performance on Y-maze test and motor tasks; performance on locomotor test; hypothetic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 2012</td>
<td>C57BL/6-ME7 Salmonella i.p. (0.1)</td>
<td>0–26</td>
<td>equivalent levels: IL-1β, TNF-α, IL-6</td>
<td>Performance on T-maze test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Griffin 2013</td>
<td>C57BL/6-ME7 IL-1β i.p. (0.015)</td>
<td>0–26</td>
<td>COX-1, COX-2, mPGES1, PGE2 (b); COX-2, mPGES-1 transcript, microglial activation (number); piroxicam, sc-560, IL-1RA</td>
<td>Performance on T-maze test (fluctuating symptoms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis 2015</td>
<td>C57BL/6-ME7 Salmonella i.p. (0.1)</td>
<td>0–26</td>
<td>Performance on T-maze test; IL-1β, TNF-α, IFN-β transcript; microglial activation (number + LPS-induced IL-1β)</td>
<td>Performance on T-maze test # donepezil; performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Field 2012</td>
<td>C57BL/6 – hypo cholinergetic model</td>
<td>Poly I:C (12)</td>
<td>Performance on T-maze (fluctuating symptoms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joshi 2014</td>
<td>3 × Tg-AD E. coli i.p. (0.5) 2 × a week for 6 weeks</td>
<td>6 w</td>
<td>IL-1β, IFN-γ P51, PEN2 transcript; tau pathology; microglia and astrocyte activation by LPS</td>
<td>Performance on T-maze test # donepezil; performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Field 2010</td>
<td>C57BL/6-ME7 Salmonella i.p. (0.4)</td>
<td>0–24, 6 w</td>
<td>Equivalent levels: IFN-β, TNF-α, IL-6</td>
<td>Hypothermic response; performance on motor tasks (acute + chronic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combrinck 2002</td>
<td>C57BL/6-ME7 Salmonella i.p. (0.5)</td>
<td>3,15</td>
<td>IL-1β, IL-6, TNF-α, TGF-β1 transcript; neuronal apoptosis (TUNEL, caspase-3); microglial activation</td>
<td>Performance on locomotor test, hypothetic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murray 2011</td>
<td>C57BL/6-ME7 Salmonella i.p. (0.5)</td>
<td>3,4,15</td>
<td>IL-1β, IL-6 # dexamethasone</td>
<td>Performance on locomotor test, hypothetic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kitazawa 2005</td>
<td>3 × Tg-AD E. coli i.p. (0.5) 2 × a week for 6 weeks</td>
<td>1 w</td>
<td>IL-1β transcript; Tau pathology; microglial activation by LPS (number + LPS-induced IL-1β); dopaminergic neurons in SN</td>
<td>Performance on fear conditioning test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Godoy 2008</td>
<td>Wistar (rat) 6-OHDA-PD E. coli i.v. (1.36 × 10⁹ pfu)</td>
<td>6 w</td>
<td>IL-1β protein</td>
<td>Hypothermic response; performance on motor tasks (acute + chronic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sly 2001</td>
<td>Tg2576-AD E. coli i.v. (1)</td>
<td>0–18</td>
<td>IL-1β protein</td>
<td>Hypothermic response; performance on locomotor test, hypothetic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunningham 2005</td>
<td>C57BL/6-ME7 Salmonella i.p. (0.5)</td>
<td>6</td>
<td>IL-1β, TNF-α, IL-6, iNOS, PTX3 transcript; neuronal apoptosis (TUNEL); microglial activation (number + LPS-induced IL-1β); # dexamethasone no effect</td>
<td>Hypothermic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheng 2003</td>
<td>APPswe Tg-AD N/A i.p. (5) 1 × a week for 12 weeks</td>
<td>12 w</td>
<td>IL-1β, IL-6, TNF-α, TGF-β1 transcript; neuronal apoptosis (TUNEL); microglial activation (number + LPS-induced IL-1β); # dexamethasone</td>
<td>Hypothermic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raj 2014</td>
<td>Ercc1&lt;sup&gt;−/−&lt;/sup&gt; E. coli i.p. (1)</td>
<td>3,18</td>
<td>IL-1β, IL-6, TNF-α, ROS transcript; phago-cytosis; microglial activation (number)</td>
<td>Hypothermic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tha 2000</td>
<td>SAMP8 E. coli i.p. (0.2)</td>
<td>2</td>
<td>Equivalent levels: IL-1β, TNF-α, IL-6 transcript + protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvarez 2014</td>
<td>SAMP8</td>
<td>3</td>
<td>IL-6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overview of differential changes in diseased rodents relative to healthy controls when exposed to a LPS, poly I:C or IL-1β. Only changes in diseased rodents are described. Genetic background, age of rodents type, dose and site of the causative agents that induce systemic inflammation, and studied time points of each study are noted. Outcomes of studies are described as changes at the level of serum, CSF, CNS and behavior and cognition. Abbreviations: (#) treatments were examined, (i.p.) intraperitoneal, (w) weeks, (N/A) not available.
declined due to progression of underlying neurodegenerative disease. Noteworthy, progression of underlying disease was accelerated in ME7 mice challenged with LPS relative to unchallenged ME7 mice, suggesting acute LPS challenge (0.5 mg/kg) accelerates and exacerbates progression of the underlying disease (Cunningham et al., 2009). Another stimulus, poly I:C, also induced increased hypothemia in ME7 mice. Similar to LPS poly I:C induced acute impairments on motor coordination and muscle strength in ME7 mice only. Moreover, repeated poly I:C challenges induced episodes of acute impairments in motor coordination and muscle strength and accelerated the progression of the underlying disease without any effect on healthy controls (Field et al., 2010). A novel paddling T-maze test was used to determine the presence of acute working memory deficits after systemic inflammation. Acute and transient deficits in working memory were observed in ME7 mice and not in control mice challenged similarly (0.1 mg/kg). Greater and prolonged cognitive deficits were observed at 15–16 weeks of disease compared to animals at 12 weeks of disease. This data demonstrates that progression of disease increases the severity and duration of LPS-induced acute working memory deficits (Griffin et al., 2013). In this work it has also been shown that IL-1β was able to mimic the effects of LPS and systemic administration of IL-1RA protected against LPS-induced cognitive deficits, suggesting a systemic role for IL-1β. Likewise, treatment with non-specific COX inhibitors piroxicam or ibuprofen, or the selective COX-1 inhibitor sc-560 also afforded protection against LPS-induced cognitive deficits by reducing disease-induced elevated PGE2 levels (Griffin et al., 2013). In addition to the acute onset and transient symptoms of delirium another important criterion is that symptoms fluctuate over time. A recent study has mirrored this fluctuating course of acute cognitive dysfunction in ME7 challenged with LPS (0.1 mg/kg) (Davis et al., 2015). In the shallow water Y-maze test ME7 mice showed impaired performance compared to controls when challenged with LPS (0.1 mg/kg). However, preservation of long-term memory remained intact when they learned the task prior to LPS challenge. Thus, these rodents show impairments of novel information but preservation of previously acquired long-term memories (Cunningham et al., 2009). To rule out the possibility that the observed cognitive deficits are not simply due to exaggerated sickness behavior, healthy controls were treated with a 5-fold higher dose (0.5 mg/kg) of LPS in the T-maze and Y-maze. No effects on cognition were observed in control mice, whereas ME7 mice produced cognitive deficits after LPS challenge (0.1 mg/kg) (Murray et al., 2012; Cunningham et al., 2009). Acute and transient working memory deficits following LPS challenge were also found in mice with basal forebrain cholinergic lesions induced by ribosomal toxin saporin linked to the p75 neurotrophin receptor (Field et al., 2012). Administration of donepezil, an acetylcholinesterase inhibitor, reduced the cognitive deficits, suggesting that impairments induced by systemic inflammation occur via disruption of cholinergic signaling. Interestingly, these hypocholinergic mice showed no signs of exaggerated CNS inflammation or microglial priming. These findings do not exclude that primed microglia play a role in inflammation-induced cognitive impairment, but indicate that the exaggerated CNS inflammation induced by primed microglia is not paramount for the development of cognitive dysfunction. Rather, these results suggest cholinergic modulation and neuronal vulnerability as the more likely predisposing factor (Field et al., 2012). One study examined the effects of sequential LPS challenges (0.5 mg/kg) for a period of 6 weeks in 3×tg-AD mice and demonstrated impaired memory consolidation in the fear conditioning test. Thus, other neurodegenerative models than ME7 also show cognitive deficits after systemic inflammation. However, the primary aim of this study was on chronic and not on the acute effects of LPS (Joshi et al., 2014).

3.3. Aged × bacterial infection

3.3.1. Description of studies

The effects of a challenge with a bacterial strain (E. coli) on systemic and CNS inflammation and behavior were evaluated in 6/77 studies (Table 2). Multiple infectious challenges over time were not examined. In all studies rodents were injected i.p. with 250 μL containing 2.5 × 10⁹ colony forming units (CFU) of E. coli. All studies focused on rats and 5/6 studies compared aged vs. adult rodents, whereas one study evaluated solely aged rodents. In terms of reproducibility, it is worth mentioning that all these studies come from a single lab.

3.3.2. Circulating inflammatory cytokines

In total, 2/6 studies evaluated effects of systemic inflammation, induced by infection, on plasma cytokine levels (Table 2). Serum IL-1β levels were increased at 2, 4, 24 h and 4 days post-infection to an equivalent extent in aged and adult rodents (Barrientos et al., 2009, 2006). Other inflammatory mediators were not examined in this group.

3.3.3. CNS inflammation

All studies evaluated the effects of a bacterial infection on the CNS inflammatory response (Table 2). An infectious challenged produced an increase of IL-1β and IL-6 transcript and protein up to 8 days post-infection in aged rodents, whereas cytokine levels in adults rodents were restored to baseline levels at 24 h (Barrientos et al., 2011, 2009, 2006; Frank et al., 2010). The exaggerated CNS inflammatory response in the aged was also associated with reduced levels of brain-derived neurotrophic factor (BDNF) protein, a neuronal growth factor that is crucial for the formation of long-term memories (Cortese et al., 2011; Barrientos et al., 2011). One study isolated microglia and demonstrated that microglia from aged rodents stimulated with LPS ex-vivo exhibit an activated microglial phenotype, as evidenced by increased IBA-1 staining, and produce exaggerated amounts of proinflammatory cytokines relative to microglia isolated from adult rodents (Barrientos et al., 2015).

3.3.4. Behavior and cognition

Effects of a live infection on cognition was evaluated in 5/6 studies (Table 2). Aged rodents challenged with an infectious stimulus either immediately after conditioning or 4 days prior to conditioning were impaired on the contextual fear conditioning test, whereas adult rodents showed no impairments (Barrientos et al., 2006). In a subsequent study a full time course analysis was performed and it was demonstrated that these cognitive impairments in aged rodents were still present at 8 days, and resolved at 14 days post-infection (Barrientos et al., 2009). Pretreatment with IL-1RA or mifepristone, a glucocorticoid receptor antagonist, or voluntary wheel running (VWR) counteracted infection-induced cognitive impairments and this was paralleled by a reduced CNS inflammatory response (Barrientos et al., 2012, 2011; Frank et al., 2010). These findings underscore a prominent role for proinflammatory cytokines in infection-induced cognitive impairments.

3.4. Aged × surgery

3.4.1. Description of studies

The effects of a surgical intervention on systemic and CNS inflammation and behavior and cognition of aged rodents were evaluated in 25/77 studies (Table 3). Among these surgical techniques were appendectomy, laparotomy, hepatectomy, splenectomy, clamping of the upper mesenteric artery, acute myocardial ischemia reperfusion, tibial fracture and peripheral surgical wounding. One study evaluated the effects of a prior infection
Table 2
Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Aged bacterial infection (E. coli)</th>
<th>Type/dose/site of bacterial infection</th>
<th>Time points (hours)</th>
<th>Serum CNS (inflammatory mediators and microglial activation)</th>
<th>Behavioral and cognitive deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrientos 2006</td>
<td>F344xBN F1</td>
<td>E. coli i.p. (2.5 × 10^9)</td>
<td>24 m</td>
<td>IL-1β protein, IL-6 protein</td>
<td>Performance on fear conditioning test</td>
</tr>
<tr>
<td>Barrientos 2009</td>
<td>F344xBN F1</td>
<td>E. coli i.p. (2.5 × 10^9)</td>
<td>3 m</td>
<td>IL-1β protein, TNF-α</td>
<td>Performance on fear conditioning test</td>
</tr>
<tr>
<td>Frank 2010</td>
<td>E. coli i.p. (2.5 × 10^9)</td>
<td>24 m</td>
<td>IL-1β protein, TNF-α</td>
<td>Performance on fear conditioning test</td>
<td></td>
</tr>
<tr>
<td>Barrientos 2015</td>
<td>E. coli i.p. (2.5 × 10^9)</td>
<td>3 m</td>
<td>IL-1β, IL-6, TNF-α</td>
<td>Performance on fear conditioning test</td>
<td></td>
</tr>
<tr>
<td>Cortese 2011</td>
<td>E. coli i.p. (2.5 × 10^9)</td>
<td>3 m</td>
<td>IL-1β, IL-6, TNF-α</td>
<td>Performance on fear conditioning test</td>
<td></td>
</tr>
</tbody>
</table>

Owing to differential changes in aged rodents’ ability to deal with bacterial infection, only changes in aged rodents are described. Cautions background age of rodents, type dose and site of bacterial infection are included. Abbreviations: (*), only studies evaluated solely aged rodents.

3.4.2. Circulating inflammatory cytokines

In total, 7/25 studies evaluated the effects of various types of surgical interventions on plasma or serum levels (Table 3). Furthermore, one study evaluated CSF cytokine levels. Serum IL-1β, IL-6, and TNF-α were increased in aged rodents in response to a variety of surgical interventions (Sun et al., 2014; Yuan et al., 2014). Other parameters that were found to be increased in serum or plasma include renin, high mobility group box 1 protein (HMGB1), and IL-10 (Li et al., 2014; Zhang et al., 2013; He et al., 2012). Within the CSF increased levels of IL-1β and TNF-α were found post-surgery (Lu et al., 2015). These studies did not include adult controls, hampering the analysis of possible adverse effects of aging. There was only one study that included controls, and equivalent levels of plasma IL-6 in aged and adult rodents after surgical intervention were observed in this study (Hovens et al., 2013).

3.4.3. CNS inflammation

In total, 24/25 studies evaluated effects of surgical interventions on the CNS inflammatory response (Table 3). Eight studies determined solely effects of anesthesia on CNS inflammation. All of the surgical interventions mentioned above resulted in increased CNS inflammation. Aged rodents that were subjected to surgery showed increased transcript and protein levels of IL-1β, IL-6, TNF-α, and IFN-γ with respect to adult rodents that underwent a similar surgical intervention (Wang et al., 2015; Barrientos et al., 2012; Cao et al., 2010; Rosczyk et al., 2008). Microglial cells of aged rodents were activated by surgery, as evidenced by an increase in IBA-1 positive cells, whereas surgery did not affect the activation of microglia of adult rodents (Le et al., 2014; Xu et al., 2014; Hovens et al., 2013). Furthermore, ex vivo stimulation of aged isolated microglia with LPS resulted in greater production of proinflammatory cytokines compared with microglia isolated from adult rodents (Kawano et al., 2015). This age-related response is in line with the concept of microglial priming. One study demonstrated increased astrocyte activation at 31 up to 35 days after partial hepatectomy, as evidenced by an increased number of GFAP-positive astrocytes (Jin et al., 2014). It is known that inflammation can modulate synaptic plasticity of the brain under pathological conditions. One study demonstrated that age differentially affects the loss of neuronal dendritic spine in rodents after surgery. As expected, aged rodents, compared to adults, showed an increased loss of neuronal dendritic spine following surgery (Le et al., 2014). Numerous other studies also demonstrated increased CNS inflammation, microglial activation and neuronal apoptosis in the brains of aged rodents (Li et al., 2015; Qian et al., 2013a; Wang et al., 2013; Peng et al., 2012). However, no efforts were made to compare these findings with adult counterparts. Inflammatory and neurotoxic mediators examined by these studies are listed in Table 3. An increase in blood brain barrier (BBB) permeability may facilitate CNS inflammatory processes. Two studies described disrupted BBB integrity and increased permeability in response to surgery (Li et al., 2014; He et al., 2012). Again, these studies did not incorporate adult controls. Inhalation anesthetics are widely used in the surgical setting. Therefore, studies also assessed whether exposure to solely anesthetics would affect CNS inflammation. Four studies demonstrated that administration of anesthetics did not alter the production of inflammatory mediators in the CNS (Qian et al., 2015; Li et al., 2013b; Cao et al., 2010; Rosczyk et al., 2008). In contrast, other studies have shown...
<table>
<thead>
<tr>
<th>Study</th>
<th>Genetic background</th>
<th>Age (months)</th>
<th>Type of surgery</th>
<th>Time points (days)</th>
<th>Serum</th>
<th>CNS (inflammatory mediators and microglial activation)</th>
<th>Behavioral and cognitive deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosczyk 2008</td>
<td>BALB/c</td>
<td>4–6 m 23–25 m</td>
<td>Laparotomy</td>
<td>1</td>
<td>IL-1β transcript</td>
<td>Performance on morris water maze reversal test</td>
<td></td>
</tr>
<tr>
<td>Cao 2010</td>
<td>Sprague-Dawley (rat)</td>
<td>3–6 m 20–24 m</td>
<td>Partial hepatectomy</td>
<td>1,3,7</td>
<td>IL-1β, TNF-α, IL-6 transcript + protein</td>
<td>Performance on morris water maze reversal test</td>
<td></td>
</tr>
<tr>
<td>Hovens 2015a</td>
<td>Wistar</td>
<td>25 m</td>
<td>Clamping upper mesenteric artery</td>
<td>10–14</td>
<td>microglial activation (morphology, number)</td>
<td>Performance on morris water maze test (probe)</td>
<td></td>
</tr>
<tr>
<td>Kong 2015</td>
<td>Sprague-Dawley</td>
<td>20 m</td>
<td>Anesthesia only 4 h isoflurane 1.3%</td>
<td>4, 14</td>
<td>IL-1β protein, + neuronal apoptosis</td>
<td>Performance on morris water maze test (probe)</td>
<td></td>
</tr>
<tr>
<td>Le 2014</td>
<td>Sprague-Dawley</td>
<td>2 m 18 m</td>
<td>Partial hepatectomy</td>
<td>1,3,7</td>
<td>IL-1β, TNF-α protein, + dendritic spine density</td>
<td>Performance on morris water maze test (probe)</td>
<td></td>
</tr>
<tr>
<td>Li 2014</td>
<td>Sprague-Dawley</td>
<td>20 m</td>
<td>Laparotomy</td>
<td>3,6,12 h, 1,7d</td>
<td>renin</td>
<td>Performance on morris water maze test (probe)</td>
<td># candesartan</td>
</tr>
<tr>
<td>Jin 2013</td>
<td>C57BL/6</td>
<td>19 m</td>
<td>Partial hepatectomy</td>
<td>31–35</td>
<td>IL-1β, TNF-α, IL-6 transcript + protein</td>
<td>Performance on morris water maze test (probe)</td>
<td># minocycline</td>
</tr>
<tr>
<td>Kong 2013</td>
<td>Sprague-Dawley</td>
<td>20 m</td>
<td>Anesthesia only 4 h isoflurane 1.3%</td>
<td>4, 14</td>
<td>IL-1β protein, + neuronal apoptosis (caspase-3)</td>
<td>Performance on morris water maze test (probe)</td>
<td># minocycline</td>
</tr>
<tr>
<td>Wang 2013</td>
<td>Sprague-Dawley</td>
<td>22–23 m</td>
<td>Splenectomy</td>
<td>1,3,7</td>
<td>TLR-4, IL-1β, TNF-α, MYD88, TRIF transcript + protein</td>
<td>Performance on morris water maze reversal test</td>
<td></td>
</tr>
<tr>
<td>Li 2013</td>
<td>Sprague-Dawley</td>
<td>20 m</td>
<td>Partial hepatectomy</td>
<td>1,3,7</td>
<td>IL-1β, TNF-α, IL-6 transcript</td>
<td>Performance on morris water maze reversal test</td>
<td></td>
</tr>
<tr>
<td>He 2012</td>
<td>Sprague-Dawley</td>
<td>22–23 m</td>
<td>Splenectomy</td>
<td>1,3,7</td>
<td>HMGB-1</td>
<td>Performance on morris water maze reversal test</td>
<td></td>
</tr>
<tr>
<td>Zhao 2011</td>
<td>Sprague-Dawley</td>
<td>18 m</td>
<td>Laparotomy</td>
<td>1–5</td>
<td>IL-1β, TNF-α, HMGB-1, RAGE transcript + protein</td>
<td>Performance on morris water maze test (lactency + distance)</td>
<td># lithium</td>
</tr>
<tr>
<td>Lu 2015</td>
<td>Sprague-Dawley</td>
<td>16 m</td>
<td>Splenectomy</td>
<td>1–6</td>
<td>IL-1β, TNF-α, TLR-2, TLR-4, NF-kB transcript, # IFN-γ transcript + protein</td>
<td>Performance on morris water maze test (lactency + distance + probe)</td>
<td># lithium</td>
</tr>
<tr>
<td>Wang 2015</td>
<td>C57BL/6 J</td>
<td>3 m 18 m</td>
<td>Appendectomy</td>
<td>3,14,28</td>
<td>IL-1β, TNF-α, TLR-2, IFN-γ transcript + protein</td>
<td>Performance on morris water maze test (lactency + distance + probe)</td>
<td># lithium</td>
</tr>
<tr>
<td>Hovens 2015b</td>
<td>Wistar</td>
<td>18 m</td>
<td>Clamping upper mesenteric artery + infection Laparotomy</td>
<td>1–43</td>
<td>Trend for IL-6</td>
<td>Performance on morris water maze (probe reversal)</td>
<td>performance on novel object recognition test</td>
</tr>
<tr>
<td>Hovens 2013</td>
<td>Wistar</td>
<td>3 m 18–20 m</td>
<td>Clamping upper mesenteric artery Laparotomy</td>
<td>1–4</td>
<td>Microglial activation (Iba-1) only CA1 region</td>
<td>No effect in multiple cognitive and behavioral tests</td>
<td></td>
</tr>
<tr>
<td>Barrientos 2012</td>
<td>F344XBN F1</td>
<td>3 m 24 m</td>
<td>Peripheral surgery wounding Tibial Fracture</td>
<td>3,6,12 h, 7d</td>
<td>TNF-α, IL-6 protein + CD-33 protein</td>
<td>Performance on fear conditioning task # IL-1RA</td>
<td>performance</td>
</tr>
<tr>
<td>Xu 2014</td>
<td>C57BL/6</td>
<td>9 m 18 m</td>
<td>Peripheral surgery wounding Tibial Fracture</td>
<td>1,3,7</td>
<td>IL-1β, TNF-α, IL-6, HMGB-1 protein, + neuronal apoptosis, + BBB permeability, + HBO preconditioning</td>
<td>Performance on morris water maze test (lactency + distance + probe)</td>
<td># PEE</td>
</tr>
<tr>
<td>Sun 2014</td>
<td>Sprague-Dawley</td>
<td>20 m</td>
<td>Peripheral surgery wounding Tibial Fracture</td>
<td>1,3,7</td>
<td>IL-1β, TNF-α, IL-6, HMGB-1 protein, + neuronal apoptosis, + BBB permeability, + HBO preconditioning</td>
<td>Performance on morris water maze test (lactency + distance + probe)</td>
<td># PEE</td>
</tr>
<tr>
<td>Qian 2015</td>
<td>BALB/c</td>
<td>20–22 m</td>
<td>Splenectomy</td>
<td>1,3</td>
<td>IL-1β, TNF-α, IL-6, HMGB-1 protein, + neuronal apoptosis, + BBB permeability, + HBO preconditioning</td>
<td>Performance on Y-maze test, + performance on fear conditioning test, + HBO preconditioning</td>
<td>performance on both tests</td>
</tr>
<tr>
<td>Li 2013</td>
<td>Sprague-Dawley</td>
<td>20 m</td>
<td>Anesthesia only 6 h isoflurane 1.3%</td>
<td>1–4</td>
<td>IL-1β, IL-6, TNF-α, + JkB protein, + neuronal apoptosis (caspase-3), + minocycline</td>
<td>Performance on morris water maze test (lactency + distance + probe), + minocycline</td>
<td>performance</td>
</tr>
<tr>
<td>Kawano 2015</td>
<td>Wistar</td>
<td>2–3 m 24–25 m</td>
<td>Laparotomy</td>
<td>1</td>
<td>IL-1β, TNF-α protein, + PEE</td>
<td>IL-1β, TNF-α protein, + ex-vivo microglia</td>
<td>Performance on morris water maze test (latency + distance + probe), + minocycline</td>
</tr>
</tbody>
</table>
that anesthetics induce a 2.5-fold increase in IL-1β and TNF-α transcript and protein, and a 3-fold increase in neuronal apoptosis (Kong et al., 2015, 2013; Li et al., 2013c). These controversial effects can be explained by methods of anesthetic exposure, animal species, age, and anesthetic concentration or duration. Although anesthetics and surgery both increase CNS inflammation, the resulting CNS inflammatory response is prolonged and amplified to a greater extent after surgery (Qian et al., 2015; Wang et al., 2015).

### 3.4.4. Behavior and cognition

Effects of a surgical intervention or solely anesthetics on behavior and cognition were evaluated in 23/25 studies. Increased CNS inflammatory responses in aged mice were found to be paralleled by cognitive impairments in differential cognitive tasks. The rodent models in this group have been set up to mimic symptoms of POCD and not delirium. Nevertheless, from an etiological perspective these models are interesting for modeling symptoms of delirium, as surgery is superimposed upon the susceptible aged phenotype. Various types of surgery including clamping of the upper mesenteric artery, hepatectomy, laparotomy, splenectomy and appendectomy induced impairments in spatial learning and memory in aged rodents, as evidenced by a decreased performance on the MWM test. Route and distance traveled during the acquisition phase and percentage of time in the target quadrant during the probe trial were used as measures of cognitive performance. All studies have used a different approach and examined cognition at diverse time points. Impairments in spatial learning and memory in aged rodents that were challenged with one of the aforementioned surgical interventions have been described at 1 week (Lu et al., 2015; Le et al., 2014; Zhao et al., 2011), 2 weeks (Hovens et al., 2015a), 4 weeks (Wang et al., 2015) and even up to 5 weeks post-surgery (Jin et al., 2014). Several studies have also demonstrated that impairments in spatial learning and memory in aged rodents are present at 1 week, 2 weeks and even 4 weeks after solely anesthetic exposure (Kong et al., 2015, 2013; Wang et al., 2015). Conversely, two other studies reported anesthetics had no effect on spatial learning and memory (Hovens et al., 2013; Cao et al., 2010). Six studies evaluated whether therapeutic interventions ameliorated impairments in spatial learning and memory induced by surgery or anesthetic exposure. Prophylactic treatment with

---

**Table 4** Neuropathological features of neurodegenerative and progeria disease models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Disease</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME7</td>
<td>Prion disease</td>
<td>PrP accumulation, microglial activation, neurodegeneration, synaptic loss</td>
</tr>
<tr>
<td>Hypocholinergic model</td>
<td>Forebrain cholinergic lesions</td>
<td>Selective lesions of the basal forebrain cholinergic system by immunotoxin</td>
</tr>
<tr>
<td>Ercc1*+/−</td>
<td>Progeria/accelerated aging</td>
<td>Glial activation, synaptic plasticity, neurodegeneration</td>
</tr>
<tr>
<td>SAMP8</td>
<td>Progeria/accelerated aging</td>
<td>Production of amyloid precursor protein (APP) and oxidative damage</td>
</tr>
<tr>
<td>6-OHDA</td>
<td>Parkinson's disease</td>
<td>Striatal dopamine levels and tyrosine hydroxylase neurons in substantia nigra</td>
</tr>
<tr>
<td>Tg2576</td>
<td>Alzheimer's disease</td>
<td>Formation of Aβ plaques, gial activation, synaptic plasticity</td>
</tr>
<tr>
<td>3×Tg</td>
<td>Alzheimer's disease</td>
<td>Formation of Aβ plaques, Tau pathology</td>
</tr>
<tr>
<td>APPsw+ Tg</td>
<td>Alzheimer's disease</td>
<td>Formation of Aβ plaques, astroglisisy, synaptic plasticity</td>
</tr>
</tbody>
</table>

Various disease models on which systemic inflammation was superimposed are included in this review. In this table an overview is provided of neuropathological features of neurodegenerative and progeria disease models.
and memory 1 and 3 days post-surgery. Exposure to solely the safe arm. Splenectomy induced impairments in place learning rodents are subjected to a shock and are forced to navigate to learning and memory in a modified Y-maze apparatus in which tial working memory at 1 and 3 days post-surgery, which had Aged rodents showed acute impairments in mental flexibility/space in the acquisition phase. The ability of the rodents to find the position of the pool after the animals have learned the location of the plat- formation, the platform is moved to the opposite quadrant of these studies and duration of testing was not long enough to demonstrate transience. Therefore, neither acute onset or trans- sience has ever been assessed in these studies. In the reversal ver- sion of the MWM, the platform is moved to the opposite quadrant of the pool after the animals have learned the location of the plat- form in the acquisition phase. The ability of the rodents to find the new location of the platform is examined and this is a measure of mental flexibility/working memory. Moreover, this test allows investigation of whether the impairments are acute and transient. Aged rodents showed acute impairments in mental flexibility/spa- tial working memory at 1 and 3 days post-surgery, which had 374 resolved at 7 days post-surgery (Le et al., 2014; Wang et al., 2013; He et al., 2012; Cao et al., 2010; Rosczyk et al., 2008). The finding that impairments in cognition resolved 7 days post-surgery indicates that impairments have a transient nature. Hapa- tectomy, splenectomy, and laparotomy were types of surgery employed by these studies. One study examined whether a history of infection may have an influence on surgery-induced impair- ments. In this study it was demonstrated that an infection prior to clamping of the upper mesenteric artery exacerbated impair- ments in spatial learning and memory and spatial working mem- ory compared with aged rodents that only underwent surgery, and this was associated with increased microglial activation (Hovens et al., 2015b). Three studies used the contextual fear con- ditioning test to determine the effects of surgery on memory con- solidation. One study showed aged rodents exhibit decreased memory consolidation 4 days after laparotomy, and impairments were no longer present 12 days after surgery, suggesting the impairments in cognition are transient. Consistent with a previous report pretreatment with IL-1RA blocking the central signaling of IL-1β prevented both the impairment in cognition and increase in CNS inflammation (Barrientos et al., 2012). Another study demon- strated decreased memory consolidation in aged rodents 1 day after peripheral surgical wounding. Treatment with ibuprofen 7 days post-surgery ameliorated these cognitive impairments (Xu et al., 2014). Ibuprofen has been shown to attenuate CNS inflam- mation, suggesting increased CNS inflammation can induce cogni- tive impairments (Silva et al., 2009). Impairments in memory consolidation in aged rodents were also induced by tibial fracture. In this study rodents were trained in the CFC test 30 min before surgery and tested up to 1 week post-surgery. The time-frame in this experimental setting is irrelevant as memory is never consol- idated due to interference from inflammation. Hyperbaric oxygen preconditioning ameliorated this cognitive impairment together with the increase in CNS inflammation, neuronal apoptosis and compromised integrity of the BBB (Sun et al., 2014). Visual and spatial memory was evaluated in the NOR test. Impaired NOR performance was observed in aged rodents 7 days (Kawano et al., 2015) and 10 days (Hovens et al., 2015b, 2015a) post-surgery and prior infection exacerbated the impaired performance (Hovens et al., 2015b). Preoperative environmental enrichment (PEE) attenuated the impairment in NOR performance (Kawano et al., 2015). During these experiments activity or motivation was not suppressed, as the total object exploration time in the NOR test was not affected by infection or surgery (Hovens et al., 2015b). Further, age did not suppress motivation, as the total exploration time during the training phase did not differ between the age groups (Kawano et al., 2015). One study assessed place learning and memory in a modified Y-maze apparatus in which rodents are subjected to a shock and are forced to navigate to the safe arm. Splenectomy induced impairments in place learning and memory 1 and 3 days post-surgery. Exposure to solely anesthetics also caused impairments in place learning and memory in aged rodents but resolved after 3 days, suggesting this effect was transient (Qian et al., 2015). Dexmedetomidine, a selective alpha 2 adrenergic receptor agonist, counteracted the detrimental effects of surgical intervention and anesthetics on Y-maze performance and this was associated with a reduced expression of CNS inflam- mation and neuronal apoptosis (Qian et al., 2015). Finally, one study assessed spatial working memory in the eight-arm radial water maze. Aged rats that were subjected to acute myocardial ischemia reperfusion (AMIR) demonstrated acute and transient impairments in spatial working memory, persisting up to 4 days post-surgery and resolving at 5 days post-surgery. Electroacupuncture (ER) reduced CNS inflammation and neuronal apoptosis and ameliorated the cognitive impairment (Yuan et al., 2014).

4. Discussion

The major aim of this systematic review was to analyze mechanistic and behavioral and cognitive processes in potential rodent models for its applicability in unraveling potential pathophysiologi- cal processes in delirium, and ultimately elaborate on how the outcome of these experiments in rodent models can be translated to clinical symptoms of delirium in humans. In this systematic review, we have demonstrated that aged and diseased rodents develop exaggerated sickness behavior and also produce greater and protracted cognitive deficits in response to systemic inflam- mation, which is associated with an exaggerated production of CNS inflammatory cytokines. Systemic inflammation-induced behavioral and cognitive deficits were consistent across different behavioral, and learning and memory paradigms, present in different species, and replicated by administration of various agents including LPS, SEA, poly I:C, IL-1β, bacterial infection or multiple types of surgical intervention (Fig. 3). The majority of studies have been set up to investigate effects of systemic inflammation on behavior and cognition in susceptible aged and diseased rodents, and therefore do not directly address delirium. Nevertheless, these are still important models to consider as they superimpose sys- temic inflammation upon highly vulnerable rodents, and combina- tion of these elements increase the risk of delirium in humans. To acknowledge that these models are effective at the translational level they should be accurate at mimicking clinical features of delirium on multiple domains including related changes at the pathophysiological, behavioral and cognitive level in humans. In this part, we will discuss systemic inflammation-induced patho- logical, behavioral and cognitive changes in aged and diseased rodents and where possible compare them to pathophysiological and clinical symptoms of delirium in humans. Furthermore, we will also provide suggestions and opportunities for future preclin- ical and clinical research into delirium pathophysiology.

4.1. Circulating inflammatory markers in serum, plasma, and CSF

Aged rodents challenged with a relatively mild LPS dose (0.33 mg/kg) showed an increased IL-6 peripheral inflammatory response compared to adult rodents challenged with an equivalent dose (Godbout et al., 2008; Berg et al., 2005). Similarly, a trend towards an age-dependent increase for IL-6 plasma cytokine levels was observed in aged rodents that underwent minor surgery. Consis- tent with these findings, a clinical study demonstrated that aged patients that received surgical treatment have higher IL-6 serum levels with respect to middle-aged surgical patients (Thaeter et al., 2016). This may be explained, at least in part, by the ampli- fied production of proinflammatory cytokines by aged peripheral blood mononuclear cells (PBMCs) (Fagiolo et al., 1993). Elevated IL-6 and IL-8 serum cytokine levels have also been shown to asso-
ciate with delirium in acutely admitted elderly- and hip-fracture surgery patients (Egberts et al., 2015; MacLullich et al., 2011; de Rooij et al., 2007). However, clinical association studies cannot demonstrate that inflammatory mediators are causal in delirium. In contrast, ME7 prion diseased rodents challenged with LPS (0.1 mg/kg) showed equivalent levels of peripheral cytokines compared to controls, suggesting a susceptible brain and not exaggerated levels of systemic cytokines are responsible for exaggerated CNS inflammation and cognitive deficits observed in ME7 rodents (Murray et al., 2011). In support of this view, healthy controls injected with a 5-fold higher dose of LPS did not show an exaggerated increase in CNS inflammation or cognitive deficits (Cunningham et al., 2009). However, ME7 rodents may not show exaggerated peripheral cytokine levels compared to controls because they exhibit disease specific changes in the brain due to extracellular prion protein deposition, but do have any other age- or disease-related changes in PBMCs at the peripheral level. It also seems reasonable to study these findings at the CSF level, as novel clinical evidence implicates an early rise of IL-1β levels in CSF of delirious patients (Cape et al., 2014). To date, only one preclinical study demonstrated increased CSF levels of IL-1β and TNF-α in aged rodents that underwent splenectomy, and these were associated with cognitive deficits (Lu et al., 2015). A wealth of clinical studies has implicated altered levels of inflammatory and neurotoxic mediators including neopterin, S100β, C-reactive protein, IL-6 and serotonin metabolites in both serum and CSF to be associated with delirium (Hall et al., 2011; Burkhart et al., 2010; van Munster et al., 2010). To our knowledge, the majority of these parameters have not been studied in rodent models. Whether these alterations can also be found in rodent models deserves future investigation.

4.2. CNS inflammation

Primed microglia were observed in aged, diseased and progeroid rodent models. Microglia were defined as primed when: (1) an activated morphology was observed by immunohistochemical staining, or (2) microglial number and size were increased, or (3) an increased expression of a specific microglial marker was found. At basal conditions (i.e. unstimulated conditions) the synthesis of proinflammatory cytokines is kept at a minimal level. However, primed microglia can be switched by systemic inflammation to a proinflammatory state with deleterious consequences. Exaggerated CNS inflammation was observed in both aged and diseased rodents challenged with systemic inflammation compared to adult or healthy rodents challenged similarly (Barrientos et al., 2011; Cao et al., 2010; Cunningham et al., 2009; Chen et al., 2008). Exaggerated CNS inflammation in aged and diseased rodents was observed irrespective of the type of infection or surgical intervention that was used to induce systemic inflammation. Furthermore, LPS and various types of surgery exacerbated neuronal apoptosis in aged rodents (Qian et al., 2015; Richwine et al., 2008). These findings
are consistent with the observation of increased neuronal apoptosis in ME7 rodents challenged with LPS (Cunningham et al., 2005). Additionally, exacerbation of neurodegeneration has also been shown in a rodent model of PD challenged with cytokine IL-1β (Pott Godoy et al., 2008). In AD rodent models chronic LPS challenge resulted in increased Aβ and tau pathology (Joshi et al., 2014; Sheng et al., 2003). These data clearly demonstrate that systemic inflammation accelerates and exacerbates progression of underlying disease. In addition to microglial activation there also appears to be a role for astrocytes and CNS inflammation in the aged and diseased brain. Increased astrocyte activation was observed in aged rodents challenged with LPS or heptapectomy (Fu et al., 2014; Cao et al., 2010). Furthermore, microglial activation appears to be present in the initial phase after surgery, whereas astrocyte activation starts at 35 days post-surgery, suggesting activated astrocytes may play a pivotal role in long-lasting CNS inflammation (Jin et al., 2014). In accordance with these findings, it has recently been demonstrated that in ME7 rodents astrocytes are primed to produce exaggerated chemokine responses after intra-hippocampal cytokine challenge (Hennessy et al., 2015). In clinical studies increased activity of both microglia and astrocytes have been shown to associate with delirium. A post-mortem study has demonstrated that systemic infection, in the form of sepsis, may result in microglial activation (Lemstra et al., 2007). Moreover, another post-mortem study indicating an association between occurrence of delirium and increased activity of microglia, astrocytes and IL-6 is in line with the findings of association of exaggerated CNS inflammation and cognitive deficits in rodent models (Munster et al., 2011). To our knowledge other factors that contribute to increased CNS inflammation in rodents have not yet been researched in delirious patients, pointing at translational gaps.

4.3. Behavioral and cognitive paradigms and treatment effects

Exaggerated sickness behavior and cognitive deficits are associated with exaggerated CNS inflammatory responses in aged and diseased rodents challenged with systemic inflammation. Analogies between exaggerated sickness behavior in aged and diseased rodents and delirium are extensively reviewed elsewhere (Cunningham and Maclullich, 2013). Delirious episodes in patients are of acute onset, transient and fluctuate with time. It is known that delirious patients perform worse on tasks that require retention and processing of novel and trial-specific information compared to patient with dementia (Hart et al., 1997). Studies have addressed the effects of systemic inflammation on multiple domains of cognitive functioning by using various cognitive tests. Until now, only the ME7 prion disease model has demonstrated acute, transient and fluctuating impairments in working memory, because this was the only rodent model in which cognitive function was evaluated by the T-maze test (Davis et al., 2015). This cognitive test is appropriate to study fluctuation of symptoms, as it is sensitive for repeated testing. Other rodent models have shown acute impairments or acute and transient impairments in cognition (Yuan et al., 2014; He et al., 2012; Chen et al., 2008). However, cognitive tests employed by these studies including the MWM reversal, 5- and 8-arm RWM, and the NOR-test are unfit as they are ill suited to repeated testing. Therefore, these tests have a limited applicability to study cognitive symptoms during delirium. Cognitive deficits in aged and diseased rodents that suffered a systemic inflammatory insult have also been demonstrated in the CFC, Y-maze, and the MWM-test (Le et al., 2014; Sun et al., 2014). However, these are not the most informative types of tests to study cognitive impairments during delirium, as reference memory and not processing of novel information, working memory, is measured. Although an attentional set is required for performing cognitive tasks, all of the previous discussed paradigms predominantly focus on cognition and less so on attention. In addition to cognitive impairments delirious patients also show symptoms of decreased attention. Until now, only one study demonstrated that during the AST-test, which examines attention and mental flexibility, aged rodents challenged with LPS show decreased attention (Culley et al., 2014). The AST-test and other paradigms that measure attention are relevant to study attentional deficits in potential rodent models for delirium. Various treatments have been used to reverse or protect against behavioral and cognitive deficits induced by systemic inflammation. Here, we will discuss a few treatments as they provide essential information on possible causal pathways that might lead to delirium. Systemically administered IL-1RA protected against LPS-induced working memory deficits in ME7 rodents, suggesting a systemic role for IL-1β. This study also showed that systemic IL-1β is sufficient to trigger cognitive deficits, suggesting IL-1β is causative in inducing cognitive deficits in the degenerating brain (Griffin et al., 2013). In contrast, another study in which rodents were subjected to laparotomy peripherally injected IL-1RA had no protective effect, whereas intracisternal administration of IL-1RA blocked both the cognitive deficit and the CNS inflammatory response. These data suggest a specific role of central IL-1β in cognitive deficits (Barrientos et al., 2012). These results are consistent with a study showing that intracisternal administration of IL-1RA blocks the increase in central IL-1β and IL-6 in aged rodents challenged with a bacterial infection, which was paralleled by a reduced cognitive deficit (Frank et al., 2010). Furthermore, other treatments including sc-560 and piroxicam afforded protection against LPS-induced cognitive deficits by reducing disease-elevated PGE2 levels in ME7 prion rodents, suggesting disease-elevated PGE2 levels are important for inducing cognitive deficits (Griffin et al., 2013). Resveratrol, minocycline, lithium and several other treatments were also effective in reducing cognitive deficits by attenuating the CNS inflammatory response (Table 1–3). Taken together, these findings provide evidence for an essential role of CNS proinflammatory cytokines in inducing cognitive deficits.

4.4. Validity check and future directions

It is well established that underlying neurodegenerative disease and aging are predisposing risk factors that interact with systemic inflammation induced by infection or surgery to produce delirium. All previously discussed models appropriately address these factors and therefore can be considered to achieve pathogenic validity (Box 1). An important point to stress here is that live infection and surgery can be considered preferable over LPS, as both precipitating factors add multiple layers of complexity and are more reminiscent of the clinical setting. Furthermore, the resulting CNS inflammatory response is amplified to a much greater extent after LPS challenge (Hoogland et al., 2015). In addition, the bolus of LPS is also short acting. For these reasons, the clinical relevance of using LPS in rodent models is questionable. Not a single model meets criteria for mechanistic validity, shared similarities of underlying biological mechanisms, because research at the pathophysiological level in patients is minimal. Although there is one clinical study providing evidence that microglia activation and other inflammatory mechanisms are involved in delirium, but this study needs to expand in size as it used a rather small patient group (Munster et al., 2011). Future studies should focus on determining the activation state of microglia in acute post-mortem brain material of patients that experienced a delirious episode. Along with post-mortem studies new diagnostic techniques including advanced positron emission tomography (PET) and single-photon emission computed tomography (SPECT) imaging can be used to elucidate the inflammatory status of microglia during and following a delirious episode in living subjects. Additionally, these
techniques with advanced tracers might also allow examination of alterations in relevant neurotransmitters, as dopamine and acetylcholine are believed to be critical players in the pathogenesis of delirium. Further, deleterious effects of inflammatory mediators on neuronal cells and function must also be examined, as preclinical studies provide evidence of increased neuronal apoptosis after systemic inflammation (Qian et al., 2015). These and additional suggestions for future research are listed in Box 2. It has been demonstrated in these rodent models that systemic inflammation interacts with aging or neurodegenerative disease to produce cognitive deficits. Nonetheless, only the ME7 model has shown acute, transient and fluctuating impairments in cognition, and thus meets criteria for ethiological validity (Davis et al., 2015). Other models have demonstrated neither transient or fluctuating symptoms as they were subjected to cognitive tests that are ill suited to repeated testing. As mentioned previously, the majority of these studies were not set up to directly address delirium. Future studies must determine whether models of different inflammatory origin combined with an aging or disease background are able to replicate these acute, transient and fluctuating impairments in cognition. Therefore, these models must be evaluated by the same and most appropriate cognitive test for delirium, referred to as the T-maze test. Although, acute, transient and fluctuating impairments in cognition is a symptom of delirium, it is not the only symptom of delirium. Decreased attention is also an important neurobiological feature of delirium, and has been demonstrated in aged rodents challenged with LPS subjected to the AST-test (Culley et al., 2014). Another suitable attentional test is the 5-choice serial reaction time test (SCSRTT) in which rodents have to correctly identify which one of the five apertures briefly illuminated, via a nose poke, to receive a food reward. It is important to demonstrate these attentional deficits as this will yield a more complete representation of delirium in rodents. Furthermore, other associated symptoms of delirium including disturbances in circadian rhythm and sleep must also be addressed in rodents. Criteria for biomarker validity are not met by rodent models, because currently there are no accurate biomarkers for delirium. However, it is worth mentioning that elevated IL-6 serum levels have been found in both delirious patients that were acutely hospitalized and aged rodents following systemic inflammatory challenge (Godbout et al., 2008; de Rooij et al., 2007). Essentially, rodent models serve as models to predict the efficacy of treatments. The ME7 model can be considered to achieve proper induction validity, as there is a relation between triggering factors and the occurrence of cognitive symptoms of delirium. Remission validity signifies that the model responds to treatments in a similar fashion as patients. It is practically impossible to determine remission validity, because currently there are no proper or licensed treatments for delirium. Numerous treatments and interventions in rodents effectively reduced cognitive deficits, but there is minimal overlap at this level between preclinical and clinical research. To enhance remission validity, future studies should investigate treatments that are adjusted to one another. Anti-inflammatory compounds effectively inhibited the production of CNS proinflammatory cytokines and this was associated with reduced cognitive dysfunction in rodents (Jin et al., 2014; Abraham and Johnson, 2009b). Hence, it is imperative to study potential effects of different anti-inflammatory compounds in delirious patients. Vagal nerve stimulation also decreased the production and release of proinflammatory cytokines through the cholinergic anti-inflammatory pathway in both rodent models and cerebral palsy patients (Xiong et al., 2009). Future clinical and preclinical studies should examine whether vagal nerve stimulation is able to attenuate symptoms of delirium by decreasing the inflammatory response.

Box 1: Values and limitations of rodent models for delirium.

Current values
1. Rodent models recreate various etiological processes (pathogenic validity)
2. Rodent models show overlapping biochemical and neuropathological features (mechanistic validity)
3. Rodent models exhibit a significant degree of behavioral pathology reminiscent of symptoms observed in delirious patients (face validity)
4. Rodent models show acute and transient changes in cognition with a fluctuating course observed in ME7 rodents
5. Increased IL-6 serum levels in aged rodents challenged with LPS overlap with increased IL-6 serum levels in patients
6. Microglial and astrocyte activation is present in both patients and rodent models
7. Rodent models challenged with LPS show acute changes in cognition, attention and executive function

Current limitations
1. Not every etiological group is reconstructed in preclinical research (construct validity)
2. Disease models are neither challenged with live infection or surgery
3. It is unknown whether rodent models precisely recapitulate crucial biochemical or neuropathological features, because there is minimal overlap between animal and clinical studies. (face validity)
4. CSF is examined in the patient and only one preclinical study evaluated CSF levels
5. Serum or plasma is examined in the patient and to a lesser extent in rodent models
6. CNS inflammation is well examined in rodent models and scarcely in clinical studies
7. Not all neurobiological and associated features of delirium are examined in rodent models (face validity)
8. Working memory has not yet been examined in aged rodents challenged with bacterial infection
9. The ME7 model does not show a temporal overlap with clinical delirium (24 h versus ± 2–5 days, respectively)
10. A fluctuating course of acute cognitive dysfunction has not yet been demonstrated for aged rodents challenged with LPS or surgery
11. Associated features including disorganized thinking, altered arousal and sleep-wake cycle disturbances are not evaluated in any of the models yet
12. Attention is only examined in aged rodents challenged with LPS
13. There is minimal overlap between drug treatments in patients and rodent models (predictive validity)
14. Drugs and interventions examined in rodent models do not overlap with drugs examined in clinical trials
Box 2: Future research to improve translation and reverse translation.

Clinical research
1. Examine CNS inflammation in delirious patients via neuroimaging or post-mortem studies to explore overlapping features with rodent models
   - PET- or SPECT-imaging to determine activation status of microglia and astrocytes in delirious patients
2. Apply treatments tested in rodent models to delirious patients and determine whether delirious patients respond in a similar fashion
   - Examine effect of anti-inflammatory compounds in delirious patients that demonstrated to improve cognitive function in rodent studies
   - Assess effectiveness of vagus nerve stimulation in delirious patients

Preclinical research
1. Examine whether clinically researched parameters of CSF and serum can be reversely translated to rodent models
   - Multiple parameters including neopterin and C-reactive protein have not been studied in rodent models
2. Investigate alternative communication routes that could be causal for increased CNS inflammation
   - Rodent models of neuropathic pain demonstrate that nerve injury results in activation of microglia, implicating an alternative route
3. Explore other parameters than solely microglia activation and production of proinflammatory cytokines
   - Examine interaction of primed microglia with synapses and neurons
   - Determine whether other myeloid cells (perivascular macrophages, blood-derived monocytes) play a role in producing CNS cytokines
4. Extrapolate AST-test or the 5-CSRTT to multiple other rodent models to determine features of decreased attention
   - Thus far, only one study demonstrated that LPS challenge results in decreased attention in aged rodents
5. Investigate multiple other associated behavioral features of delirium in rodent models
   - Sleep-wake cycle disturbance and altered arousal are associated features which are not studied in rodent models yet
6. Develop rodent models that superimpose surgery or live infection upon disease
7. Establish rodent models that demonstrate a temporal overlap with clinical delirium
   - Rodent models employing live infection or surgery may show a more realistic temporal overlap than rodents challenged with LPS
8. Examine whether rodent models respond to treatments in a similar fashion as patients
   - Study the effects of antipsychotics and benzodiazepines on delirium-associated symptoms in rodent models
9. Elucidate epigenetic signatures of primed microglial cells
   - Epigenetic signatures may possibly clarify inter-individual variation in the onset and progression of delirium

4.5. Limitations

There are some limitations that must be acknowledged. This systematic review only included studies that superimposed systemic inflammation upon aging or disease. According to a basic classification proposed by Macullich et al., there are two major distinct causes that might explain delirium: direct brain insults and aberrant stress responses (Macullich et al., 2008). Our systematic search also included rodent models of drug-induced delirium, which can be considered as direct brain insults. Anticholinergic drugs were able to induce polygraphic- and behavioral changes consistent with clinical delirium (Tamura et al., 2006; O’Hare et al., 1997; Leavitt et al., 1994; Trzepacz et al., 1992). These studies were not included because systemic inflammation was not induced. Another limitation is that we have not systematically assessed effects of systemic inflammation in young or healthy rodents, which can develop delirium-like symptoms when exposed to serious events like severe sepsis. We have chosen the approach to only address the effects of systemic inflammation in aged and diseased rodents, because aged and demented patients are at a substantially increased risk for delirium of systemic inflammatory origin.

5. Conclusions

In sum, this review provides a comprehensive overview of potential rodent models for delirium and relevant underlying biological mechanisms. Currently, there is no definite rodent model covering all symptoms of delirium. However, the ME7 model has proven to be a well-established rodent model, as there are parallels between the type of cognitive impairment present during delirium and those in the ME7 model. Other models that superimpose systemic inflammation on aging or disease might show similar cognitive impairments when interrogated by the same cognitive test. As delirium is not only represented by impairments in cognition further refinement of current model systems is an important priority for future research. Attentional aspects and circadian rhythm and sleep-wake cycle disturbances warrant further investigation in the near future. Future preclinical and clinical research addressing pathophysiology and treatment of delirium and its symptoms should be aimed at minimizing demonstrated gaps in translation. Ultimately this will result in an increased overall validity of potential rodent models and proper translation to address this important clinical problem, affecting many elderly hospital patients in a frail state who currently receive medication for delirium symptoms without exact knowledge on the long-term effects on neuroinflammation. We expect that increased insight into neuropathological, behavioral and cognitive changes will move the field of delirium research and clinical practice ahead and ultimately boost the efficacy of target-centered approaches to drug discovery for delirium and preserving brain function.

Funding

This work was supported by an unrestricted grant from the UMCG.

Author disclosure statement

There are no actual or potential competing interests.

Acknowledgments

We thank Dr. Nynke Smidt for providing helpful advice on how to conduct a systematic review and Dr. Colm Cunningham for providing critical feedback on an earlier draft.


