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REVIEW

The neuroinflammatory hypothesis of delirium

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Abstract Delirium is a neuropsychiatric syndrome characterized by a sudden and global impairment in consciousness, attention and cognition. It is particularly frequent in elderly subjects with medical or surgical conditions and is associated with short- and long-term adverse outcomes. The pathophysiology of delirium remains poorly understood as it involves complex multi-factorial dynamic interactions between a diversity of risk factors. Several conditions associated with delirium are characterized by activation of the inflammatory cascade with acute release of inflammatory mediators into the bloodstream. There is compelling evidence that acute peripheral inflammatory stimulation induces activation of brain parenchymal cells, expression of proinflammatory cytokines and inflammatory mediators in the central nervous system. These neuroinflammatory changes induce neuronal and synaptic dysfunction and subsequent neurobehavioural and cognitive symptoms. Furthermore, ageing and neurodegenerative disorders exaggerate microglial responses following stimulation by systemic immune stimuli such as peripheral inflammation and/or infection. In this review we explore the neuroinflammatory hypothesis of delirium based on recent evidence derived from animal and human studies.

Introduction

Delirium is a common neuropsychiatric syndrome clinically characterized by a sudden onset and transient impairment of consciousness and attention, with consecutive global disturbance in cognition and behaviour. It affects predominantly elderly subjects, with reported rates depending on the sample and setting considered, being associated with both short- and long-term adverse outcomes [94]. Thus, in medical in-patient settings, the occurrence rate per admission is 11–42% [125]. In elective orthopaedic surgery the incidence of postsurgical delirium ranges from 9 to 28% [145]. Higher rates are seen in emergent hip fracture surgery in which a large proportion of patients present with pre-operative (4–36%) or post-operative delirium (up to 53%) [19]. Post-operative delirium after cardiac surgery varies from 2 to 57% according to the procedure, type of patients and study methodology [22, 138]. In the context of sepsis, delirium affects 9–71% of patients [37].

As with other neuropsychiatric disorders, the pathophysiology of delirium remains poorly understood for a number of reasons. First, the core features of delirium (impaired level of consciousness and inattention) are difficult to define and to operationalize. Secondly, the protean nature of delirium with respect to clinical symptoms, severity and evolution challenges its recognition. Thirdly, delirium has significant aetiological complexity reflecting the dynamic interaction of multiple environmental and individual factors. Finally, the inaccessibility of the central nervous system (CNS) limits the exploration of the neurobiological correlates of the high integrative cognitive

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functions globally affected during delirium. Not surprisingly, despite its clinical relevance, delirium has been a relatively neglected area of research. However, considering that delirium is a syndrome in which the link between brain and body is most clear, ongoing advances in the understanding of the interaction between the CNS and peripheral organs through bloodstream herald important breakthroughs in the study of its pathophysiology.

In this study we explore the contribution of the neuroinflammatory pathway to delirium. First, evidence associating systemic inflammation with delirium is presented. Then, we review the sequence of events explaining the relation between acute systemic inflammatory stimulation and delirium. Given the absence of neuropathological studies in humans during the acute phase of delirium, animal models provide the best available opportunity to study the neurobiological correlates of acute cognitive and behavioural dysfunction following systemic inflammation. Whenever possible, evidence obtained from human studies is discussed. Studies evaluating the effect of the ageing process and neurodegeneration are also analysed in order to elucidate how these two known major risk factors for delirium are involved in its pathophysiology. Finally, we present some future perspectives on how these concepts can be useful to develop new therapeutic measures to prevent delirium. Taken together, these data provide a framework with heuristic value to guide new approaches in the study of delirium.

Delirium concept

Clinical definition of delirium

Following the landmark work of Engel and Romano [42], delirium has been conceptualized as a reversible state of cerebral insufficiency comparable to the more familiar concepts of renal or hepatic insufficiency. Although this clinical syndrome was one of the first mental illnesses to be recognized, its nosologic classification remains a continually evolving process. This is reflected in the scientific literature by the use of a confusing plethora of terms referring to conditions that are embraced in the concept of delirium as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [5] or in the tenth edition of the International Statistical Classification of Diseases and Related Health Problems [146]. Often, different labels are used specifically in some settings to describe the condition at a clinical (e.g. acute confusional state) or pathophysiological level (e.g. encephalopathy and acute brain failure). This reveals both the multifaceted nature of delirium and the lack of a consistent approach to this syndrome.

Currently, delirium is defined in DSM-IV-TR [5] by the presence of disturbed consciousness (i.e. reduced clarity of awareness of the environment with reduced ability to focus, to sustain, or to shift attention) and a change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. There is evidence from clinical history, physical examination, and/or laboratory findings that the disturbance is caused by direct physiological consequences of a general medical condition [5].

In addition to these core symptoms, associated clinical findings include disturbance in psychomotor function, speech (thought process), sleep-wake cycle and mood. In clinical practice, it is common to classify delirium as: (a) hypoactive subtype, characterized by reduced alertness, sedation and reduction of motor activity; (b) hyperactive form, associated with hyper-vigilance, psychotic features (e.g. hallucinations and delusions) and agitation; and (c) a more prevalent, mixed subtype with overlapping features of the previous two forms. There is a lack of consensus about the definition of each subtype [33] and whether they have different underlying aetiology and pathophysiology [127]. However, there is growing evidence that hypoactive delirium is associated with worse outcomes compared to the other subtypes in elderly patients with dementia [147].

Pathophysiology of delirium

The pathophysiology of delirium involves the interplay between predisposing, precipitating and protective factors (Fig. 1). This model has been globally supported by numerous studies in medical and surgical samples which have identified several risk factors for delirium [22, 32, 69] (Table 1). Results from these studies are difficult to summarize and generalize because they involve different settings, measurements and methodologies. However, most consistently reported variables across studies include: dementia, medical illness, advanced age, abnormal blood urea nitrogen/creatinine ratio, abnormal sodium or potassium level, alcohol abuse, sensory impairment, and medications [40]. To reduce the analysis heterogeneity, it is useful to differentiate studies according to the setting (e.g. medical or surgical). Additionally, cardiac surgery has been classically distinguished from non-cardiac surgery as they differ with respect to factors with specific effects on pathophysiology of delirium such as extra-corporeal circulation or vascular dysfunction (Table 1B, C). Some studies have tried to determine the magnitude of risk associated with certain factors in order to establish the likelihood of delirium occurrence. For example, Inouye et al. [69] developed a four-factor model for risk stratification in medical patients in which presence of 1 or 2 factors had a 4.7-fold increase in risk of delirium, while having 3 or 4 factors was

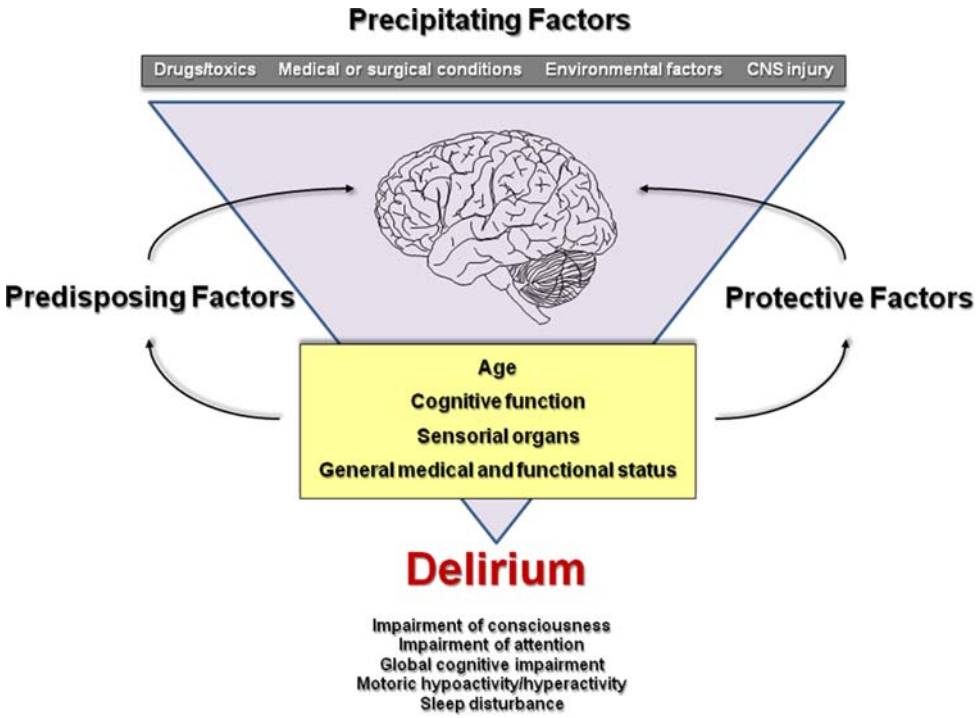

Fig. 1 Multifactorial model of delirium

associated with a 9.5-fold risk (Table 1A). When applied to a non-cardiac surgical sample, this model proved to have good reliability [70].

Consequently, from a pathophysiological point of view, it is possible to conclude that in most cases of delirium there is interaction of multiple precipitating and predisposing factors, each one increasing the risk only marginally. While providing a general view about the pathogenesis of delirium, this does not elucidate the particular aetiological role of each risk factor. Given the small individual effect sizes of the several identified risk factors, delirium pathophysiology is likely to involve the interaction of multiple systems eliciting neurochemical abnormalities and brain dysfunction. Thus, cholinergic dysfunction has long been recognized to be involved in delirium pathophysiology and has been proposed as a "final pathway" to delirium regardless of the initial insult [133]. Other proposed hypothesis for delirium pathophysiology includes decreased oxidative metabolism, dysfunction of other neurotransmitters (dopamine, norepinephrine, glutamate, serotonin, and GABA), abnormal signal transduction, changes in blood-brain barrier (BBB) permeability, endocrine abnormalities and increased inflammatory response [87].

Clinical conditions with systemic inflammatory reactions to induce delirium

Systemic inflammation is a prominent feature of numerous medical and surgical conditions associated with delirium, particularly when they involve tissue destruction and/or infection (Table 2). Thus, delirium is a frequent manifestation of a multiorganic dysfunction in the context of sepsis [124], a presenting clinical feature of underlying urinary tract infection or pneumonia (especially in demented elderly patients) or a complication following a major surgical procedure [102].

Peripheral infection activates the inflammatory cascade following direct recognition of specific components of microorganisms, such as lipopolysaccharide (LPS) in gram-negative bacteria, by resident and circulating phagocytes. A myriad of factors, such as tissue damage, blood loss, pain and anaesthetics can influence the function of immunocompetent cells and production of inflammatory mediators [78]. Even in a sterile setting, inflammation can be triggered following tissue destruction with the release of endogenous ligands, including heat shock proteins, hyaluronan, β-defensin and uric acid crystals which will activate similar innate receptor pathways [8]. Proinflammatory cytokines produced by resident macrophages and monocytes, including tumour necrosis factor alpha (TNF-α) and interleukin (IL)-1, will, in turn, stimulate the expression of other mediators responsible for the recruitment of additional inflammatory cells to the injured site. Thus, what initially can be a localized immune reaction spreads to a generalized, systemic response with increased levels of cytokines in the circulation [12, 76] (Table 2). In cardiac surgery, cardiopulmonary bypass appears to be a major factor for activation of complement and secretion of proinflammatory cytokines contributing to post-operative

Table 1 Factors reported to be associated with increased risk of delirium

(A) Medical setting [69]	
Visual impairment	Severe illness
Cognitive impairment	Dehydration
(B) Post-operative delirium (cardiac surgery) [22]	
Cerebrovascular disease	Diabetes mellitus
Peripheral vascular disease	Preoperative atrial fibrillation
Impaired left ventricular ejection fraction	Preoperative cardiogenic shock
Urgent operation	Intraoperative hemofiltration
Prolonged duration of surgery	High blood transfusion requirement
(C) Post-operative delirium (non-cardiac surgery) [32]	
Cognitive impairment	Older age
Functional impairment	Sensory impairment
Depression	Preoperative psychotropic drug use
Psychopathological symptoms	Medical comorbidity

Table 2 Medical or surgical conditions in which systemic inflammation is a feature of the pathophysiological process (see references for details)

Systemic illness
Infection (e.g. sepsis, urinary tract, pneumonia, and abscess) [123, 144]
Trauma [50, 83], surgery [12, 76]
Burns [71]
Neoplasm (primary, metastasis and paraneoplastic syndrome) [80]
Cardiac
Myocardial infarction [90], cardiac surgery [6]
Haematological
Leukaemia, stem cell transplant [129]
Renal
Renal failure [128]
Hepatic
Hepatitis, cirrhosis, hepatic failure [121]
Orthopaedic
Fractures [140]

multi-organ dysfunction [6]. Reversely, off-pump procedures are associated with a lesser degree of plasmatic inflammatory mediators and improved function of major organs and post-operative cognitive performance [35]. Elevated levels of peripheral inflammatory mediators also correlate with post-operative organ dysfunction in non-cardiac surgical procedures [53].

In many other medical or surgical conditions, in which delirium is a common occurrence, the release and production of pro-inflammatory mediators into the circulation is part of the pathophysiological process (Table 2). The extent to which a certain condition activates the inflammatory cascade depends on several factors, namely the intensity of physical/surgical trauma and the likelihood of certain procedures to promote the release and diffusion of inflammatory mediators through the bloodstream (e.g. highly vascularized organs) [114]. Evidence directly implicating acute systemic inflammation in the occurrence of delirium comes from a study in which blood levels of IL-6 and IL-8 were higher in patients with post-operative delirium than in patients without delirium [140]. However, the clinical correlate of the peripheral inflammatory reaction, particularly to what extent it contributes to neuropsychiatric symptoms, has remained largely unexplored.

Effects of acute systemic inflammation in the brain

From acute systemic inflammation to neuroinflammation

It is now well established that CNS resident cells react to the presence of peripheral immune signals, leading to production of cytokines and other mediators in the brain, cell proliferation and activation of hypothalamus–pituitary–adrenal axis through a complex system of interactions [31]. This innate response constitutes an important adaptive advantage because it coordinates a central response to combat acute peripheral infection. Several pathways involved in this communication include: (a) direct recognition of pathogenic signals or inflammatory mediators in areas where BBB is altered or absent; (b) energy-dependent transport systems for cytokines in the BBB or second messengers actively produced in the BBB; (c) detection of peripheral immune activation by specialized sensory nerves carrying information into the brain via autonomic nervous system [63].

Disruption of blood-brain barrier

Animal studies consistently show that peripheral inflammatory stimuli are associated with functional and molecular

Table 3 Functional and molecular changes in blood-brain barrier following acute systemic inflammatory stimuli

Reference	Intervention	Results
Huber [68]	Formalin (5%)	Increased [^{14}C]sucrose uptake at 1 h
		Increase in ZO-1 expression at 1 h
	λ-Carrageenan (3%)	Increased [^{14}C]sucrose uptake
	CFA (50%)	Increase in ZO-1 and actin expression
		Decrease in occluding expression
Huber [67]	Pentobarbital sodium + λ-carrageenan (3%)	Increased [^{14}C]sucrose uptake at 1, 3, 6 and 48 h
		Increased expression of ZO-1 at 1, 3 and 6 h
		Decreased expression of occludin at 1, 3, 6, 12 and 48 h
Brooks [17]	CFA (50%)	At 72 h, decreased occludin expression and increased expression of claudin 3 and 5. No changes in expression of ZO-1 and actin compared to controls
		At 72 h increase in [^{14}C]sucrose uptake
Brooks [18]	CFA (50%)	Increased [^{14}C]sucrose brain uptake at 24 and 72 h
		Decreased expression of occludin at 72 h
		Increased expression of JAM-1 at 48 h and decreased expression at 72 h
		Decreased expression of claudin 5 at 24 h, increased expression at 48 and 72 h
Huber [66]	λ-Carrageenan (3%)	Increased expression of ICAM-1 in cerebral microvessels
		No change in systemic proinflammatory cytokines during the early phase (1–6 h). Early microglia activation (3 h). Increased levels of IL-1 and IFN-γ at 48–72 h
McCaffrey [92]	λ-Carrageenan (3%)	Reduced amount of oligomeric occludin in cerebral microvessels

In each experiment 100 µl of the inflammatory agent was subcutaneously injected into the plantar surface of the right hind paw of female rats
CFA complete Freund's adjuvant

changes in BBB. Increased BBB permeability and altered expression of tight-junctional proteins were reported in three different inflammatory models (Table 3). Similarly, peripheral injection of LPS (the most commonly used model of acute systemic inflammation) induces, at very early stages, a cascade of events leading to BBB disruption, over-expression of adhesion molecules in endothelial cells, recruitment and infiltration of blood-derived leucocytes into brain tissue [61, 100, 118] (Table 4). Post-mortem studies in human brain tissue also show considerable correlation between systemic inflammation and activation of endothelial and perivascular cells [135]. Although neuropathological confirmation of BBB disruption in human subjects is difficult to obtain, elevated blood levels of the β subunit of S100 protein (S100-β) can be considered as an evidence of increased BBB permeability [89]. Thus, several conditions associated with acute systemic inflammation (e.g. septic shock and cardiac surgery) are presumably associated with BBB dysfunction [2, 48, 99]. Likewise, BBB disruption during episodes of delirium can be inferred from a recent study showing elevated serum levels of protein S100-β in acutely ill elderly medical patients with delirium [139]. Also, delirium during the early phases of septic shock is associated with leucoencephalopathy in brain magnetic resonance imaging (MRI), suggestive of BBB breakdown [119]. In addition to systemic inflammation, other factors affect the BBB microscopic structure and function, including hypoxia, ischaemia and pain [93, 104]. Conditions where these factors occur simultaneously (e.g. sepsis and surgery) are then more likely to promote the leakage of inflammatory agents circulating in the plasma through the BBB (Fig. 2).

Reactions of CNS mediated by molecules from systemic circulation

In the CNS, a diversity of blood-borne molecules, including LPS, are able to interact directly with receptors located on brain endothelial and parenchymal cells. Microglial cells are particularly capable to detect changes in CNS environment through a vast number of surface and nuclear receptors [82, 103]. Thus, in mice CNS, cells lining the large blood-vessels and microglia express the Toll-like receptor 4 (TLR4; receptor for LPS). Its activation is a key-step for the elaboration of a CNS inflammatory response after administration of peripheral LPS [24]. There is also evidence that other mediators are implicated in the communication between the periphery and the brain, including TNF-α and monocyte chemoattractant protein 1 [1, 107, 131] (Table 4). Once activated by receptor–ligand interaction, microglia exhibit, over a period ranging from minutes to few hours, morphological changes alongside

Table 4 Animal studies: neuroinflammation following acute systemic inflammation

Author	Sample	Intervention	Results
Gautron [49]	8-week-old rats (250–300 g)	LPS i.p. (250 μg/kg)	Increased expression of markers of astrocyte activation (STAT3) in areas lacking BBB at 2 h after treatment, with subsequent propagation to hypothalamus, cortex, corpus callosum and hippocampus
Semmler [118]	Male rats (250–300 g; age not specified)	LPS i.p. (10 mg/kg)	Increased iNOS expression in the striatum, hippocampus, midbrain and cerebellum, at 24 h, compared to controls. Increased number of astrocytes in the cortex, striatum and hippocampus. Increased expression of apoptotic markers in the cortex, hippocampus, midbrain and cerebellum
Qin [107]	TNF R1/R2+/+ mice (8 weeks old; 20–22 g)	LPS i.p. (5 mg/kg)	Increased levels of brain TNF-α mRNA and protein with a peak at 60 min. Elevated levels of TNF-α protein in the brain at 14 days, 21 days and 10 weeks; Microglia activation in cortex, hippocampus and substantia nigra
		TNF-α i.p. (0.25 mg/kg)	Increased levels of brain TNF-α mRNA and protein. Increased synthesis of other pro-inflammatory factors
	TNF R1/R2−/− mice (8 weeks old; 20–22 g)	LPS i.p. (5 mg/kg)	TNF-α not detected in the brain
		TNF-α i.p. (0.25 mg/kg)	TNF-α not detected in the brain
Alexander [1]	TNFR+/+ mice (8 weeks old)	LPS i.p. (0.15 mg)	Increased levels of TNF-α and TNFR1 mRNA in the brain, especially in the hippocampal region
	TNF R1−/− mice (8 weeks old)	LPS i.p. (0.15 mg)	Less apoptosis, less neutrophil infiltration, less astrocytosis, less iNO mRNA expression compared with TNFR+/+ mice
Thompson [131]	MCP-1+/+ mice (20–25 g; age not specified)	LPS i.p. (5 mg/kg)	Increased levels of MCP-1 in the serum and brain up to 24 h compared to saline controls
			Increased levels of IL-1β and TNF-a in plasma, entorhinal cortex, frontal cortex and hippocampus compared to saline controls
	MCP-1−/− mice (20–25 g; age not specified)	LPS i.p. (5 mg/kg)	Increased levels of IL-1β and TNF-a in plasma compared with LPS-treated MCP-1+/+ mice
			Increased levels of IL-1β and TNF-a in entorhinal cortex, frontal cortex and hippocampus compared to saline controls but lower than in LPS-treated MCP-1+/+ mice
Nishioku [100]	8-week-old mice	LPS i.p. (20 mg/kg)	Increased BBB permeability, microglial activation, structural alterations in pericytes and basal lamina of the hippocampus

BBB blood-brain barrier, *iNOS* inducible nitric oxide synthase, *LPS i.p.* lipopolysaccharide intra-peritoneal, *MCP-1* monocyte chemoattractant protein-1, *TNF R1/2* TNF-α receptor 1/2. Whenever appropriate, the genotype of the animals is indicated with −/− (knockout) or +/+ (wild-type)

with expression of several molecules including MHC class I, CD45, CD4, ICAM-I, VLA-4, LFA-1 and Fas [79, 82] (Fig. 2). Following stimulation, some subpopulations of microglia also express MHC class II and B7 molecules [98]. These changes are coupled with microglial production of proinflammatory cytokines (TGF-β1, IL-1β, TNFα, IGF-1), reactive oxygen species (ROS) and expansion of microglial population through proliferation of resident cells and recruitment from adjacent areas or blood [14].

The initial recognition of peripheral inflammatory stimuli in the BBB is followed by a cascade of events leading to a coordinated modulation of adjacent cells and structures of the neurovascular unit [26] (Table 4; Fig. 2). Endothelial cells, astrocytes, microglia, pericytes and basal lamina interact through a wide range of mediators including cytokines, chemokines and metalloproteinases [23]. Astrocytes are most important in propagating signals generated in the neurovascular unit to other brain regions exerting a multimodal control on synaptic transmission, neuronal excitability and cerebral blood flow [141].

Acute systemic inflammation and neurocognitive dysfunction

Systemic inflammatory insults are associated not only with full-blown delirium but they are also implicated in more subtle neuropsychiatric symptoms. Symptoms similar to but not meeting the criteria of full delirium have long been recognized in people treated with recombinant IFN [88] and occurrence of sub-syndromal delirium has been associated with adverse outcomes in elderly individuals [27]. In healthy human subjects experimental treatment with bacterial

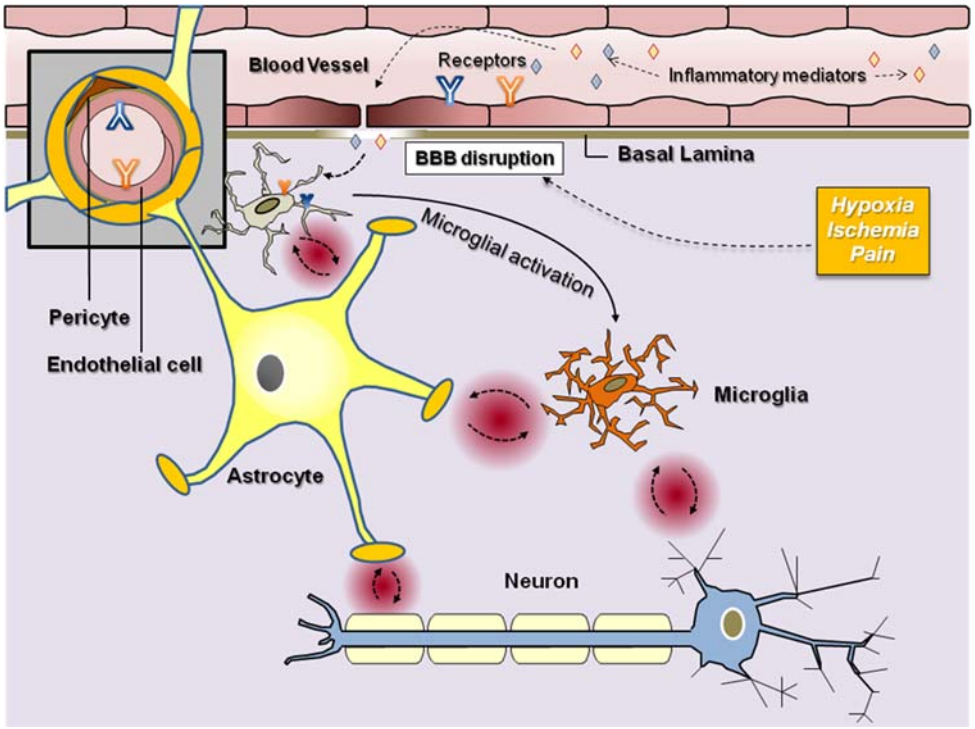

Fig. 2 Recognition and propagation of peripheral immune stimuli in the CNS. The initial interaction of circulating inflammatory mediators (e.g. cytokines and lipopolysaccharide) with the neurovascular unit occurs through a vast number of receptors and is associated with an increased paracellular permeability of the blood-brain-barrier. In addition to systemic inflammation, other factors affect the integrity of BBB including hypoxia, ischaemia and pain. Recognition of peripheral inflammatory stimuli in the BBB is followed by a cascade of events leading to microglia activation and subsequent modulation of adjacent cells including astrocytes and neurons (represented with *dashed reciprocal arrows*)

endotoxin produces a dose-dependent effect in cognitive function, emotional state and sleep [96, 110]. Circulating cytokines are increased by very low dose LPS (0.2 ng/kg) and these changes have a negative impact in declarative memory [75]. More recently, a study using functional MRI documented that injection of peripheral LPS in healthy volunteers evoked a sustained systemic inflammatory reaction and psychomotor retardation in cognitive tasks and this correlated with enhanced activity in the left substantia nigra (SN) [21].

Similarly, the elegant series of rodents' studies using LPS, cytokines and surgical procedures established that peripheral immune stimulation induces an acute and transient state characterized by sleepiness, anorexia and apathy together with cognitive impairment [132]. These symptoms are part of the sickness behaviour syndrome, reproducing the acute neurobehavioural response to infection. It should be stated in advance that aspects of the experimental design used in animal studies have potential confounding factors affecting the data interpretation [28]. Also, significant obvious differences exist between the complexity of cognitive, emotional and behavioural repertoires between rodents and humans. So, rather than being used as comprehensive models to mimic the multiple aspects of delirium, animal experiments can be useful in examining the pathophysiology underlying particular neurobehavioral responses to acute systemic inflammation.

Animal experiments using several learning and memory paradigms have consistently shown that peripheral immune system activation has a significant impact on cognition. For example, impairments in memory consolidation of previously learned tasks and disruption of working memory were reported in animals following LPS-induced immune stimulation [105]. Temporary impairment in spatial learning and memory, coupled with microglial activation and expression of proinflammatory cytokines, was also described in animals undergoing splenectomy. These changes were not observed in rats devoid of intervention and those with anaesthesia only [143] (Table 5).

Cognitive changes following acute systemic inflammation are thought to result from cellular and molecular synergic interactions in different brain regions and particularly in the hippocampus. Pro-inflammatory IL-1 has long been recognized to impair hippocampal-dependent fear conditioning and to have an important role in neurophysiological processes of memory consolidation, possibly modulating synaptic plasticity [109]. IL-6 has also been implicated in hippocampal dysfunction [126] (Table 5). In contrast, IL-10 seems to counterbalance the effects of IL-1 and IL-6, inhibiting behavioural and cognitive consequences of peripheral inflammation [77, 112] (Table 5). Likewise, decreased hippocampal decreased expression of brain-derived growth factor (BDNF) and increased oxidative stress with mitochondrial dysfunction have also been implicated in deficits of learning and memory associated with neuroinflammation [101, 130]. These data suggest that the combined action of locally brain produced ROS, proinflammatory cytokines, metalloproteinases, NO

Table 5 Animal studies: acute systemic inflammation and neurocognitive dysfunction

Author	Sample	Intervention	Results
Sparkman [126]	IL-6+/+ rats (3–5 months old)	LPS i.p. (100 μg)	Increase in plasma IL-1β, TNF-α, IL-6 and IL-10
			Impairment performance in a matching-to-place task in the water maze at day 2 after compared with saline-injected rats
			Increased expression of IL-1β and TNF-α in the hippocampus
	IL-6−/− rats (3–5 months old)	LPS i.p. (100 μg)	Increase in plasma IL-1β, TNF-α, IL-6 and IL-10
			No impairments in performance in the water maze compared with controls
			No increased expression of IL-1β and TNF-α in the hippocampus
Tanaka [130]	Male rats (age and weight not specified)	Intra-hippocampal LPS for 5 consecutive days (20 μg/day)	Increased expression of IL-1 and TNF-α at 2 h co-localized with microglia
			After sub-acute treatment with LPS for 5 days animals presented memory and learning deficits in a passive avoidance task, long-term activation of microglia and decreased expression of BDNF and TrkB
Noble [101]	10- to 12-week-old mice (35–40 g)	LPS i.p. (250 μg)	Memory impairment in a Y-maze test
			Increased ROS and NO production associated with GSH depletion in brain mitochondria
Wan [143]	90-day-old rats (300–350 g)	Anaesthesia only	No differences from control rats. No glial activation
		Splenectomy	Impaired cognitive performance, microglial activation and increased production of IL-1β mRNA in the hippocampus at post-operative days 1 and 3
Krzyszton [77]	IL-10+/+ mice (3 and 12 months old)	LPS i.p. (10 μg)	Motor performance and learning not different from controls receiving saline
			Increased levels of IL-1β, TNF-α, and IL-6 in cerebellum, cortex, hippocampus and striatum compared to controls
	IL-10−/− mice (3 and 12 months old)	LPS i.p. (10 μg)	Deficits in motor performance and learning compared with animals injected with saline
			Increased levels of IL-1b, TNF-α, and IL-6 in cerebellum, cortex, hippocampus and striatum compared to IL-10−/− animals receiving saline, with markedly higher levels than in LPS-treated IL-10+/+ animals in 3 of 4 brain regions
Lee [81]	25–30 g male mice (age not specified)	LPS i.p. (250 μg/kg)	Cognitive impairment in passive avoidance test and water maze test
			Increased levels of Aβ1-42 and decreased levels of Aβ1-40 in the hippocampus
			Increased expression of APP, BACE and C99 with increased activity of β and γ-secretase in the cortex and hippocampus
			Increased number of activated astrocytes and apoptotic cells in the hippocampus
Richwine [112]	IL-10+/+ (3-month-old mice)	LPS i.p. (10 μg)	Reduced locomotor behaviour at 4 h and recovering to 72% of controls at 24 h
			Increased expression of IL-1, IL-6 and TNF-α in the hippocampus, hypothalamus, cortex and cerebellum
			Reduced expression of hippocampal BDNF
	IL-10−/− (3-month-old mice)	Saline i.p.	Lower levels of BDNF in the hippocampus compared to saline-injected IL-10+/+ mice
		LPS i.p. (10 μg)	Reduced locomotor behaviour at 4 h with 35% of controls at 24 h
			Cytokine levels significantly increased compared with LPS-treated IL-10+/+ mice at 4 h
			Expression of hippocampal BDNF significantly lower than LPS-treated IL-10+/+ mice
			Impaired performance in a matching-to-place task in the water maze at 24 h

APP amyloid precursor protein, *BACE* β-site APP cleavage enzyme, *BDNF* brain-derived neurotrophic factor, *GSH* reduced glutathione, *LPS* lipopolysaccharide, *ROS* reactive oxygen species. Whenever appropriate, the genotype of the animals is indicated with −/− (knockout) or +/+ (wild-type)

and chemokines induce functional changes in neurons, affecting processes such as synaptic plasticity and long-term potentiation, and can impair learning and memory [91].

There is evidence that microglia and astrocyte activation by peripheral immune challenge can promote Bax/Bcl-2 imbalance and affect intraparenchymal brain cell survival [118]. In fatal cases of septic shock, Sharshar et al. [120] found neuronal and glial apoptosis within the cerebral autonomic centres in human brains, which correlated with the expression of endothelial inducible nitric oxide synthase (iNOS). Lee et al. [81] suggested that the activation of amyloidogenesis associated with neuroinflammation could be an important mechanism implicated in the apoptotic neuronal death and neurocognitive dysfunction induced by systemic immune stimuli (Table 5). The cascade of events occurring within the CNS following peripheral immune stimulation can affect neuronal viability even at long term. Thus, a single exposure to systemic LPS or TNF-α induced a significant loss of dopaminergic neurons in the SN first observed at 7 months (23% loss) and showing increasing severity at 10 months after the insult (47% loss) [107].

Overall, these data demonstrate that acute exposure to systemic inflammation elicits a neurocognitive clinical syndrome analogous to delirium coupled with an underlying neuroinflammatory reaction affecting synaptic and neuronal function. As the synthesis of acetylcholine is particularly sensitive to homeostatic changes in the brain, neuroinflammation promotes a cholinergic deficit with associated imbalances in other neurotransmitters including dopamine, serotonin and norepinephrine [64]. The current scientific knowledge cannot fully explain the exact mechanisms by which these structural, functional and neurochemical changes are translated into cognitive, behavioural and emotional symptoms. Data from anaesthetics demonstrate that some core symptoms of delirium (e.g. impaired consciousness) likely involve changes in dynamic aspects of neuronal activity affecting brain's ability to integrate information through functional disconnection between different anatomical structures [3]. Also, distinct clinical features may arise due to impairment of brain areas known to be the neuroanatomical substrates of alertness, awareness and attention [149]. It is also possible that the neuroinflammatory pathway may only be responsible for some specific symptoms of delirium.

Effects of acute systemic inflammation in the brain: influence of ageing and neurodegeneration

Individuals with advanced age and/or with prior cognitive impairment (including dementia) are at greater risk of developing delirium. There is also increasing evidence that the occurrence of delirium predicts adverse cognitive outcomes at long term in subjects with or without pre-existing dementia [46, 86]. This suggests that delirium and dementia share overlapping pathophysiological features which arise in the context of the ageing process, the common risk factor to both conditions. It is therefore of major interest to explore the influence of ageing and neurodegenerative conditions in the CNS response to systemic inflammation.

Effects of acute systemic inflammation in the ageing brain

Several aspects of the innate and cellular immunity are affected as age increases, a process known as "immunosenescence" [52]. Elderly individuals show a weaker adaptive immunity rendering them more prone to infection and less responsive to vaccination or experimental treatment with LPS [20, 41]. At the same time, the ageing process is associated with a sustained two- to fourfold increase in baseline levels of circulating inflammatory mediators including cytokines and acute phase proteins [74].

Cognitive performance is generally preserved in human normal ageing apart from a slowed processing speed and impairment in spatial memory [148]. Several neuropathological, cellular and molecular changes are associated with ageing, including a decline in brain volume and weight, loss of synaptic density and plasticity as well as variable changes in dendritic branching [136]. Studies in cognitively intact elderly show a strong positive correlation between age and altered tau protein metabolism with accumulation of neurofibrillary tangles and a variable deposition of corpora amylacea, argyrophilic grains, neuromelanin, and lipofuscin in various brain regions [72, 95]. Equally important is the finding of an increased number of activated, enlarged or dystrophic microglia in the aged brain of non-demented subjects paired with immunophenotypic changes such as up-regulation of MHC class II [47]. While it remains controversial whether these cells represent an activated rather than a senescent state, it is clear that microglial cells undergo age-related morphological and functional changes which can induce a pro-inflammatory environment in the aged brain [13]. It is likely that this microglial "primed" state with increased reactivity is the consequence of several factors including chronic accumulation of minor insults resulting in DNA damage and in the production of advanced glycation end products of tissue and cell surface proteins [36].

Neuropathological evidence linking neuroinflammation to clinical signs of brain dysfunction is illustrated by a case-report in which widespread neuroinflammatory changes

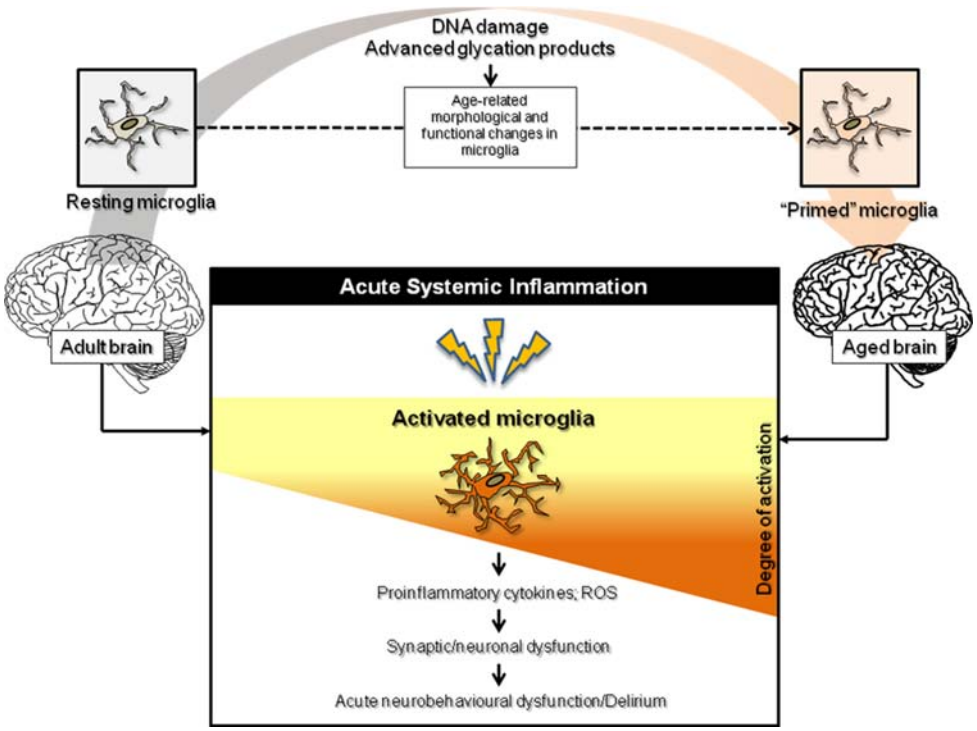

Fig. 3 The effects of acute systemic inflammation in the brain: the influence of ageing

induced by relapsing polychondritis were responsible for clinical features of Dementia with Lewy bodies [54]. Similar reports are useful to explore the neuropathological correlates of chronic, but not acute, systemic inflammatory conditions in an aged non-degenerative brain. Thus, animal studies remain the only way to document in detail how the ageing process can influence the CNS response to acute systemic inflammation (Fig. 3).

As in humans, brains of aged mice devoid of neurodegenerative disease show an increased expression of genes associated with heightened microglial reactivity [108]. Following peripheral administration of LPS, old mice show a delayed recovery from sickness behaviour, compared to adult animals, reflecting an exaggerated and protracted neuroinflammatory response [51] (Table 6). These findings were replicated following administration of intracerebrovascular LPS [65] which, by excluding any potential cytokine amplification at the periphery, support that ageing is associated with increased CNS immune responsiveness (Table 6). Chen et al. [25] reported that old mice consistently showed higher basal levels of microglia density and inflammatory cytokines in the hippocampus compared with their young adults counterparts. Peripheral inoculation of LPS increased hippocampal expression of cytokine mRNAs (IL-1, IL-6, TNF-α) in both groups (old and young adults), but significantly more in the old mice. Furthermore, old mice treated with LPS showed the most severe disruption in hippocampal capacity to integrate new information in relation to any of the other groups. In another study, Henry et al. [55] reported an increased microglial expression of MHC II in aged mice, a phenotype indicating a primed or reactive state (Table 6). Following LPS peripheral challenge, primed microglia were activated to a greater extent than MHC II-negative microglia and were highly responsible for the exaggerated production of IL-1β. These findings are in line with those of Richwine et al. [111] who found higher steady-state expression of pro-inflammatory cytokines and decreased expression of neurotrophic factors in the hippocampus of aged mice compared with adults (Table 6). This was associated with increased vulnerability of CA1 neurons to LPS-induced neuroinflammation as shown by structural changes with decreased dendrite complexity compared to adult controls. Interestingly, even minor surgical trauma was associated with increased IL-1β hippocampal expression of aged but not adult animals on the first post-operative day [113] (Table 6).

Acute systemic inflammation in dementia

Dementia is a syndrome characterized by a progressive and irreversible decline in multiple cognitive domains. This is manifested by memory impairment and other associated cognitive deficits (e.g. aphasia, apraxia, agnosia, disturbance in executive functioning) which cause significant interference in social and occupational functioning [5].

Patients with dementia represent up to 42% of all admissions in acute medical wards mainly due to urinary tract or respiratory infections [115]. Delirium complicates

Table 6 Animal studies: the effects of acute systemic inflammation in the ageing brain

Author	Sample	Intervention	Results
Godbout [51]	3- to 6-month-old rats	Saline i.p.	
		LPS i.p. (10 μg)	Increased levels of inflammatory cytokines in the brain
	20- to 24-month-old rats	Saline i.p.	Gene transcriptional profile suggestive of primed microglia and increased inflammation in the brain
		LPS i.p. (10 μg)	Prolonged sickness behaviour and exaggerated production of brain inflammatory cytokines compared with younger animals
Huang [65]	3- to 4-month-old mice	Saline icv	
		LPS (10 ng) icv	Increased levels of IL-1β, IL-6 and TNF-α in cerebellum and hippocampus
	20- to 24-month-old mice	Saline icv	Increased expression of reactive microglial markers compared to adults
		LPS (10 ng) icv	Protracted sickness behaviour associated with prolonged cytokine overexpression compared to adults
Chen [25]	3- to 4-month-old mice	Saline i.p.	
		LPS i.p. (0.33 mg/kg)	Increased levels of inflammatory cytokine mRNA in hippocampus
	22- to 24-month-old mice	Saline i.p.	Increased number of microglial cells and higher levels of IL-1β in hippocampus compared to adult mice treated with saline
		LPS i.p. (0.33 mg/kg)	Higher levels of inflammatory cytokine mRNA in hippocampus compared to adult mice treated with LPS. Deficits in spatial working memory
Richwine [111]	3- to 6-month-old mice	Saline i.p.	
		LPS i.p. (0.33 mg/kg)	Increase in hippocampal expression of IL-1β, IL-6 and TNF-α mRNA peaking at 4 h
	22- to 24-month-old mice	Saline i.p.	Increased expression of MHC II mRNA and lower expression of NGF and BDNF in the hippocampus compared to adults
		LPS i.p. (0.33 mg/kg)	Higher levels of hippocampal pro-inflammatory cytokines compared to adults. Decreased arborisation of apical dendritic tree compared to old controls
Rosczyk [113]	4- to 6-month-old mice	Minor abdominal surgery	Increased levels of IL-1β mRNA in hippocampus of aged mice
	23- to 25-month-old mice		
Henry [55]	3- to 4-month-old mice	Saline i.p.	
		LPS i.p. (0.33 mg/kg)	Increased expression of IL-1β and IL-10 mRNA in microglia
	18- to 20-month-old mice	Saline i.p.	Increased expression of MHC II in microglia compared to adults
		LPS i.p. (0.33 mg/kg)	More pronounced increased in IL-1β and IL-10 than in adult microglia

BDNF brain-derived neurotrophic factor, *icv* intracerebroventricular, *LPS* lipopolysaccharide, *MHC* major histocompatibility complex, *NGF* nerve growth factor

24–89% of hospitalizations for elderly patients with dementia predicting poor cognitive and functional outcomes [10, 44, 94]. Therefore, differentiating delirium from pre-existing dementia is clinically relevant and has been recommended as a routine practice [16]. Classically, delirium and dementia have been differentiated based on clinical features (impaired versus clear consciousness) and natural course (rapid onset and fluctuating versus progressive onset and stable). Still, there is a substantial clinical overlap between the two conditions and the crucial issue in most cases is to identify and remove the reversible components of the clinical picture. Delirium superimposed in dementia is associated, as in non-demented patients, with deregulation of neurotransmitter systems [137]. Also, there is no strong evidence that delirium has distinct features when occurring in patients with prior dementia [134]. However, recent studies suggest that level of consciousness and hyperactive motor features can be more frequently seen among delirious demented patients than in non-demented patients with delirium [15, 38].

Chronic neuroinflammatory events are known to play an important role in dementia, particularly in AD. In fact, one of the hallmarks of AD is presence of activated microglia and reactive astrocytes in Aβ plaques and neurofibrillary

tangles together with a broad variety of inflammatory mediators before the development of extensive tau-related neuropathology and brain atrophy [120]. Interaction of Aβ with microglial cell surface receptors, in the presence of synergic molecules such as complement cascade proteins, induces the activation of microglia with subsequent phagocytosis of amyloid and production of inflammatory cytokines by these cells [39]. Interestingly, the LPS receptor CD14 interacts with fibrillar Aβ suggesting that a structural mimicry exists between aggregated Aβ fibrils and pathogenic-associated microbial patterns [85]. There is evidence that microglia activation leads to a reduction in Aβ plaques supporting their neuroprotective role [30]. However, reactivity of microglia and astrocytes against Aβ can promote or exacerbate the neuropathological changes of AD [43, 97]. In fact, inflammatory conditions can impair microglial capacity for internalization of amyloid precursor protein (APP) peptides [142] and affect the expression and function of APP secretases [116] favouring the accumulation of Aβ fibrils. Similarly, microglia-derived IL-1β and IL-6 can induce tau hyperphosphorylation through activation of the p38-MAPK and cyclin-dependent kinase 5 (cdk5), respectively [73].

In addition to up-regulation of a broad variety of inflammatory mediators in the AD brain, serum levels of inflammatory markers have been associated with a risk of cognitive decline in several cross-sectional and longitudinal studies, albeit with conflicting results [4, 117]. Moreover, impaired BBB function has been implicated in several pathogenic cascades in AD [9] presumably rendering AD patients more prone to detrimental effects of acute systemic CNS inflammation. To clarify this, few attempts have been made to explore the impact of acute systemic inflammation on the natural course of AD. In a study by Holmes et al. [62], acute systemic inflammatory events were associated with a twofold increase in the rate of cognitive decline over a 6-month period. There was no association between the occurrence of those episodes with delirium (assessed at 2, 4 and 6 months) [62]. This could have resulted from the under-recognition of delirium in the sample and to the mild nature of majority of the acute systemic inflammatory events. Thus, it seems that acute systemic inflammation interferes with the natural course of AD, even if it is not severe enough to elicit delirium symptoms. Additional data on this topic is provided by Higuchi et al. [60] who, although not using specific instruments to evaluate delirium, found elevated blood levels of IL-1β in AD patients early before and during periods of agitation. Clearly, longitudinal studies documenting the immediate impact of acute systemic inflammatory episodes on the mental state of patients are needed.

Further insight about the effect of acute systemic inflammation in the pathophysiology of dementia is provided by pre-clinical research. Animals previously infected with murine prion disease as a model of chronic neurodegeneration have microglia with morphologic changes typical of activation, with altered morphology and upregulation of surface markers, but without elevated levels of cytokines or iNOS [29]. Intraperitoneal LPS injection induces an intense neuroinflammatory response in animals with ongoing neurodegeneration which is associated with neuronal death as demonstrated by increased number of TUNEL-positive cells showing apoptotic morphology [29].

Transgenic APP mouse models of AD are also useful to explore the effects of LPS treatment in neuroinflammation and amyloid deposition. While studies consistently demonstrate that LPS administration to amyloid-depositing transgenic mice results in expected neuroinflammatory changes (microglia activation, and increase of inflammatory mediators), findings regarding amyloid deposition are conflicting. Thus, some studies reported increased deposition of Aβ in mice brain parenchyma following treatment with LPS [106, 122], whereas others have demonstrated a decrease in Aβ load following LPS exposure, supporting a role for microglia in Aβ removal [34, 57, 58]. With disease progression, expression of microglial Aβ-binding receptors and Aβ-degrading enzymes is reduced and coupled with over-expression of pro-inflammatory cytokines. These changes are likely to impair Aβ processing and removal by microglia, potentially contributing to accelerate the disease course [59].

In summary, there are clinical and neuropathological evidences suggesting that pre-existing dementia significantly increases the susceptibility of CNS to the deleterious effects of acute systemic inflammation. Inversely, acute systemic inflammation can aggravate the pathophysiological changes associated with the ongoing neurodegenerative process. Although these findings have not been typically conceptualized as being central to delirium, they support an aetiological role for the neuroinflammatory pathway both in delirium and dementia, proving a pathophysiological explanation for the intimate relation between the two conditions.

Perspectives on prevention and treatment of delirium

Management of delirium involves the early identification and immediate removal of precipitating factors complemented with supportive measures and, in general, symptomatic use of neuroleptic medication is not recommended as the primary management of delirium. In some patients with hyperactive symptoms, such as agitation or hallucinations, haloperidol

remains the preferred drug but it should be used cautiously [16]. In fact, in elderly subjects with dementia, the use of anti-psychotics to control symptoms of agitation has been associated with increased mortality [7]. So, considerable interest exists whether the evidence reviewed in this paper can bring new approaches for the prevention and management of delirium. In this regard, some agents with anti-inflammatory action were useful to reduce LPS-induced microglial/astrocyte activation, production of pro-inflammatory mediators and facilitating recovery from neurobehavioural symptoms [11, 56, 84, 118]. Likewise, in models of experimental sepsis there is evidence that blockage of C5a, a small peptide derived from complement activation, can prevent BBB breakdown [45]. It remains to be determined how these findings can be applied to humans. Nevertheless, development of pharmacological strategies that can modulate the neuroinflammatory pathway may well offer new therapeutic tools to be used in the management of delirium.

Conclusions

Delirium is a complex and dynamic condition characterized by non-linear interactions among aetiologically distinct factors and by graded and continuous changes in cognitive, behavioural and emotional symptoms. Clinically, it is often difficult to recognize and to differentiate from other psychiatric disorders, as it involves subtle changes in a wide range of neurocognitive and psychomotor domains. Not surprisingly, delirium has resisted to

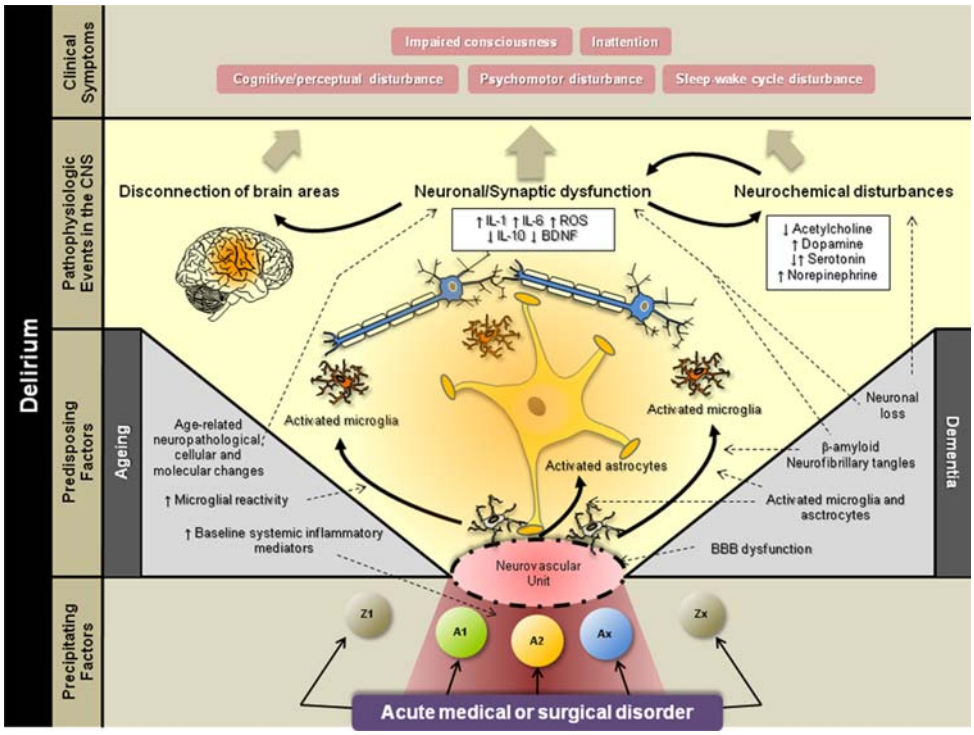

Fig. 4 The neuroinflammatory pathway of delirium. The majority of conditions associated with delirium are characterized by significant aetiological and pathophysiological heterogeneity with complex interactions of multiple factors (systemic inflammation, dehydration, electrolytic imbalance, pharmacological agents, ischaemia, hypoxia, pain, etc.). Activation of the systemic inflammatory response is a feature of several acute medical or surgical disorders, particularly when involving tissue destruction and/or infection. In such cases, numerous molecules (e.g. lipopolysaccharide and pro-inflammatory cytokines) circulating in the bloodstream (represented as *A1*, *A2*, *Ax*) elicit a cascade of functional and structural changes within the neurovascular unit leading to the activation of microglial cells and astrocytes. The acute neuroinflammatory reaction affects physiological processes implicated in neuronal and synaptic function with consequent neurochemical disturbances and functional disconnection between different anatomical structures. These neurobiological changes underlie acute and transient failure of high integrative cognitive, behavioural and emotional functions as seen in delirium. When present, other factors (e.g. dehydration, electrolytic imbalance, pharmacological agents, ischaemia, hypoxia, pain, etc., represented as *Z1*, *Zx*) while not directly activating a systemic inflammatory response, can exert synergic effects with the neuroinflammatory pathway through alternative pathophysiological routes. The contribution of the neuroinflammatory pathway to promote the symptoms of delirium is likely to be especially relevant in elderly subjects or in patients with prior dementia. As discussed in the text, several pathophysiological changes associated with both conditions render the brain more vulnerable to the deleterious effect of acute systemic inflammation (represented with *dashed arrows*). *BBB* blood-brain barrier, *BDNF* brain-derived growth factor, *CNS* central nervous system, *ROS* reactive oxygen species

the formulation of consistent etiopathogenic models able to integrate the already identified risk factors with their underlying clinical correlates.

In this review we have attempted to provide a comprehensive perspective about the contribution of the neuroinflammatory pathway in the pathogenesis of delirium. Thus, there is compelling evidence that the presence of peripheral immune signals culminates, through a complex system of communication involving the BBB, in functional and structural changes in brain parenchymal cells, including microglia, astrocytes and neurons. These neuroinflammatory changes are associated with acute onset of cognitive, behavioural and emotional disturbances. While studies in humans could provide the best evidence linking acute systemic inflammation to the specific symptoms of delirium, the research in this field remains very scarce. So, despite all the limitations, animal models are useful to evaluate the neuropathological correlates of acute psychomotor and cognitive disturbances associated with acute systemic inflammation.

By gathering data from both sources it is apparent that a neuroinflammatory response is an important event associated with delirium whenever the subject is exposed to a diverse range of peripheral conditions, especially when involving infection, tissue destruction and systemic inflammation. Brain homeostasis, neurotransmission and neurophysiological functions of several regulatory centres in the brain can be compromised by the neurotoxic effect of cytokines, ROS, NO and other inflammatory mediators, generated mainly by microglial and astrocytic cells. Predictably, when such events occur, dysfunction of cerebral cortical areas and sub-cortical structures is likely to result in a reduced capacity to interact with the environment and to integrate stimuli within the cognitive experience. This provides a plausible neurobiological rational supported by a temporal association linking neuroinflammation phenomena to the failure of high integrative cognitive, behavioural and emotional functions observed in delirium (Fig. 4).

This is further pronounced in elderly subjects and in patients with dementia. As discussed, in both cases several regulatory networks involved in neuroprotection are characteristically dysregulated and microglial cells are overactivated in baseline conditions. It is, therefore, likely that people with advanced age and/or neurodegenerative disorders would be at increased risk to develop delirium because, even when other factors are excluded, the neuroinflammatory response would be amplified due to a combination of primed microglia, increased production of pro-inflammatory mediators and decreased level of protective mechanisms (Fig. 4). Another important question is whether neuroinflammatory changes co-occurring with delirium have a role in the development of neurodegeneration and cognitive impairment at long term. As shown, evidence from clinical and animal studies reveals that beyond the acute phase, acute systemic inflammation can elicit a sustained dysregulation in neuroinflammatory events potentially aggravating pre-existing neurodegeneration and cognitive decline.

The evidence about the intricate neuroinflammatory processes underlying acute neurocognitive and behavioural symptoms following systemic inflammation insults provide powerful insight for the formulation of a comprehensive etiopathogenic model of delirium. In the context of a multifactorial, complex and dynamic model, the neuroinflammatory pathway can be a major process underlying delirium when the individual is exposed to an acute systemic inflammatory condition (e.g. infection or surgery). This model does not exclude, of course, the contribution of other factors known to be relevant to the syndrome such as hypoxia, dehydration, electrolytic imbalance and pharmacological agents. Presumably, the synergic interaction among these factors can result in a complex and simultaneous acute failure of several physiological pathways involved in brain homeostasis.

The progressive understanding of the fundamental neurobiological processes underlying delirium will allow a more precise definition and classification of this syndrome looking behind its confusing plethora of symptoms and taking into account its pathogenesis. This knowledge is also crucial to guide the search for specific and sensitive biomarkers enabling the risk stratification, the diagnosis at the pre-symptomatic stage, monitoring the clinical evolution and predicting the clinical outcome. Ultimately, this will also have implication on the development of more effective approaches to prevent the occurrence of delirium and slow the progression or retard the clinical manifestations of neurodegenerative disorders.

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