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The Immunology of Delirium

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Delirium · Inflammation · Immune response

Abstract
Delirium is an acute neuropsychiatric syndrome characterized by acute-onset global cognitive deficits, perceptual and behavioural disturbances affecting mainly elderly subjects with underlying medical or surgical conditions. The pathophysiology of delirium is complex and inflammation is a relevant precipitant factor of this syndrome, although it remains unclear how acute systemic inflammation induces the clinical picture of delirium. The central nervous system is able to detect peripheral infection or tissue destruction through circulating immune mediators and neural ascending signs. Activated microglia is responsible for an acute neuroinflammatory reaction underlying the symptoms of sickness. In healthy conditions descending pathways from the paraventricular nucleus, locus coeruleus and dorsal motor nucleus organize a centralized response to influence the immune response at the periphery and restore homeostasis. In the context of ageing and chronic neurodegeneration, adaptive changes to acute insults are characterized by exaggerated production of pro-inflammatory cytokines by primed microglia coupled with dysfunction of brain-to-immune pathways. In animal models, these changes underlie a more severe manifestation of sickness behaviour with working memory deficits suggesting that inattention, a core feature of delirium, can be a clinical correlate of an increased neuroinflammatory reaction. In patients with delirium, higher levels of pro-inflammatory cytokines and cortisol were identified in plasma and cerebrospinal fluid. However, to date it has not been clarified how peripheral inflammatory or endocrine biomarkers can reflect the likelihood or severity of delirium symptoms. In the future, a better understanding of the interaction between the brain and peripheral organs and the exact mechanism by which systemic inflammation can lead to delirium, will allow the development of new therapeutic agents.

Conceptual Overview

Delirium refers to a cluster of cognitive, emotional and behavioural symptoms developing rapidly in the context of an underlying general medical condition and/or substance use considered to be aetiologically related to the symptoms [1]. In addition to the core features of disturbed consciousness with inattention, delirium manifests with a global impairment in cognitive function (such as memory deficit, disorientation or language disturbance) and/or with perceptual disturbances which are not better accounted for by a pre-existing dementia [1]. Additionally, a range of neuropsychiatric symptoms are almost invariably present, including sleep-wake disturbance, lability of affect, delusions and motor disturbances. Delirium has typically an acute onset and symptoms fluctuate over the course of the day [2]. This syndrome is particularly common in elderly subjects with acute medi-

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cal conditions (e.g. urinary tract infection) or undergoing emergent surgical procedures. Despite being a transient disorder (lasting hours to days) delirium is associated with increased morbidity and mortality, higher risk of dementia and acceleration of cognitive decline [3–5].

Delirium Pathophysiology and Inflammation

The association between delirium and inflammation can be traced back to antiquity. In the *Hippocratic Corpus* the most frequent term associated with the current concept of delirium is 'phrenitis' which literally means 'inflammation' of the phrenes, the alleged seat of the soul [6]. Since then, and for centuries, the presence of fever has been used as a criterion to distinguish mental changes secondary to physical illness (i.e. delirium) from other conditions [7]. Currently, delirium pathophysiology is conceptualized as a state of acute and global disruption of the brain function as the result of the complex interplay between predisposing (e.g. advanced age, prior dementia) and precipitant factors. Most common precipitating factors of delirium are medications, infections, metabolic disorders, surgical procedures and primary central nervous system (CNS) disorders. Subjects with a more vulnerable brain can develop delirium when exposed to even mild noxious stimuli (e.g. urinary infection).

A useful scheme to classify aetiological factors of delirium is to consider whether there is evidence of direct brain involvement either selectively (e.g. neurological disorders) or as one of the multiple organs of the body that are involved (e.g. systemic inflammatory disorders). Many precipitant factors of delirium, while not occurring in the CNS, clearly affect essential physiological processes supporting brain function (e.g. hypoxia, anaemia, hypoglycaemia). The pathophysiological link between delirium and a broad array of infectious and inflammatory abnormalities is more difficult to establish when these conditions occur without identifiable involvement of the brain. Indeed, neither the origins of individual variability in response to inflammation nor the underlying mechanisms by which the presence of inflammatory mediators in the bloodstream results in delirium are fully understood. Moreover, how completely different aetiological causes may evoke similar symptoms has not yet been satisfactorily explained. Yet, it is well established that during threatening conditions, such as infection or injury, it is indispensable that immunological responses are integrated in the full range of homeostatic mechanisms of the body. Consequently, the CNS and the peripheral immune system maintain a dynamic cross-talk to tightly co-ordinate the innate immune response.

In this review, we will delineate the mechanisms by which the CNS senses peripheral infection and tissue damage and how it provides a complex input to the innate immune system. This is crucial for an overall understanding of how a dysregulated neural control of immunity can underlie the clinical syndrome of delirium.

Activation of the Immune and Nervous Systems following Acute Infection or Tissue Injury

Local Activation and Regulation of the Innate Inflammatory Response during Infection or Tissue Injury

The main trigger of inflammation is the recognition of highly conserved features of microbes (e.g. lipopolysaccharide, LPS, peptidoglycan) by 'pattern-recognition receptors', PRRs, expressed by resident immune cells. These PRRs include the cell-surface Toll-like receptors (TLRs) and cytosolic receptors collectively referred to as nucleotide-binding oligomerization domain-like (Nod-like) receptors. In addition, a number of endogenous molecules that are released by necrotic cells (e.g. heat shock proteins, hyaluronan, β-defensin, uric acid crystals) have been proposed to initiate the inflammatory process [8]. Activation of TLRs initiates a conserved signalling cascade that culminates in the activation of NF-κB and IFN-regulatory factor transcription factors in activated phagocytes and mast cells. Release of pro-inflammatory cytokines (particularly TNF-α and IL-1) and other inflammatory mediators by these cells induce morphological and molecular changes in the adjacent structures such as endothelial cells [9]. Within minutes to hours, circulating leukocytes, primarily neutrophils, are recruited to the site of damage and eliminate the microbe through phagocytosis [10]. Anti-inflammatory signals, including lipid-derived mediators (e.g. lipoxins, arachidonic acid derivatives) and anti-inflammatory cytokines, shift the response towards a state of resolution of inflammation and tissue clearance whenever the infection or tissue damage is controlled [9]. Appropriate regulation of these mechanisms is crucial to simultaneously protect the host and limit the damaging aspects of inflammation.

Immune Signal Transduction from the Periphery to the Brain

Being an organ crucial to survival, the brain continuously monitors the immune state of the body and reacts promptly whenever there is an acute activation of the in-

nate immune response. Multiple pathways are involved in this communication between periphery and the brain. Pro-inflammatory cytokines produced in the infected/injured organ are able to activate afferent nerves (e.g. vagus, trigeminus) which convey the signals to the brain [11]. Also, recognition of PRRs can occur directly by immune cells located in circumventricular organs of the CNS. Moreover, circulating cytokines including IL-1, IL-6 and TNF-α can be actively transported across the blood-brain barrier, thus gaining access to the brain, or interact with receptors expressed by cerebral endothelial cells inducing the production of prostaglandin E2 into the brain parenchyma [12]. Resident microglia, which in healthy conditions remain in a quiescent state, express a multitude of surface receptors able to detect immune signals initiated at the periphery. Following activation, these cells initiate a neuroinflammatory reaction with the production of pro-inflammatory cytokines including IL-1, IL-6 and TNF-α, and chemokines such as monocyte chemoattractant protein-1 able to attract monocytes from the circulation into the brain [13, 14].

The Influence of Aging and Neurodegeneration

The normal aging process is associated with a shift in the inflammatory profile of the brain towards an overall pro-inflammatory environment and increased oxidative stress. Consistent with this, the aged brain of humans and rodents shows, in baseline conditions, an increased number of microglial cells with functional, morphologic and phenotypic features suggestive of an activated state [15]. These age-related changes include upregulation of MHC class II, CD68, CD11b and CD11c integrins, TLR and co-stimulatory molecule CD86(B7) [16]. This microglia subset, referred to as 'primed', has a more exuberant cytokine production in response to systemic inflammatory signals (e.g. LPS inoculation) compared to activated microglia from adult animals [17]. The cause of this enhanced responsiveness to immune challenges is largely unknown but may involve a decreased microglial sensitivity to the anti-inflammatory signalling pathways (i.e. IL-10, TGFβ and IL-4) [15]. Additionally, the aged brain shows, in baseline conditions, reduced levels of neuronally expressed proteins such as fractalkine ligand (CX3CL) and CD200, which have been implicated in microglial regulation following acute activation. The interaction of these proteins with receptors exclusively located in microglia (CX3CR and CD200R) keep these cells in a resting state and attenuate their responsiveness to acute systemic inflammation [15, 18]. Thus, it is likely that dysfunction in several regulatory systems underlie microglial senescence which results in a diminished capacity to perform their normal function and in a more toxic environment for the neural cells [19]. Similarly, since the early stages of the disease, hippocampal microglia from murine models of neurodegeneration show a morphology and surface markers indicative of an activated state. These primed microglial cells react robustly to an acute systemic challenge with exaggerated synthesis of pro-inflammatory cytokines [13].

Descending Pathways from the Brain to the Immune System

During acute infection or injury the brain orchestrates a centralized response through activation of efferent networks including: (i) the hypothalamic-pituitary-adrenal (HPA) axis; (ii) the sympathetic nervous system (SNS), and (iii) the parasympathetic nervous system.

The HPA Axis

The paraventricular nucleus in the hypothalamus contains the corticotropin-releasing factor cells that initiate the HPA response when activated by ascending and descending signalling pathways following acute infection or injury [20]. Among a diversity of stimuli known to activate the HPA axis, cytokines are particularly able to stimulate the paraventricular nucleus acting both systemically or through paracrine/autocrine effects. Secretion of corticotropin-releasing factor into the portal venous system induces the release of adrenocorticotropic hormone (ACTH) in the anterior pituitary which in turn, when in circulation, stimulates glucocorticoid production from the adrenal cortex. Despite this axial conformation, production of glucocorticoids during acute infectious/inflammatory insults is enhanced by direct actions of cytokines within the pituitary and adrenal glands [21]. Cortisol (in humans) and corticosterone (in rodents) are powerful anti-inflammatory agents and regulate the immune response through binding either mineral corticoid receptors (type I) or glucocorticoid receptors (type II) expressed by immune cells. The sensitivity of the HPA axis to feedback inhibition by cortisol decreases with ageing [22] and with dementia severity [23], resulting in a hyperactivity of the axis and a slower recovery from acute stress. Also, increased adrenal sensitivity to ACTH has been documented in patients with dementia [24]. Thus, increased levels of plasma ACTH and plasma cortisol are expected in elderly as compared to young participants [25].

The SNS

The SNS originates in nuclei within the brain stem, including the locus coeruleus, and gives rise to preganglionic efferent fibres through the thoracic and lumbar spinal nerves. These fibres terminate primarily in the superior cervical ganglia, stellate ganglia, superior mesenteric ganglia and celiac ganglia, from which postganglionic sympathetic fibres run to the tissues innervated, including lymphoid organs. During an immune response cytokines such as IL-1, IL-6, and TNF-α can trigger activation of both the SNS and the HPA axis [26]. Activation of the SNS system leads to increased release of norepinephrine from the varicose sympathetic nerve terminals and epinephrine from the adrenal medulla. Catecholamines exert predominantly anti-inflammatory effects targeting α- and β-adrenergic receptors expressed by monocytes, macrophages and lymphoid cells [27].

The Parasympathetic Nervous System

The 'inflammatory reflex' is a neural pathway comprising both afferent and efferent fibres of the vagus nerve that senses systemic inflammation and transmits anti-inflammatory signals to modulate the innate inflammatory response at the periphery. The dorsal motor nucleus of the vagus is the origin of the descending preganglionic fibres referred to as the 'cholinergic anti-inflammatory pathway'. Activation of the vagus nerve induces the release of acetylcholine at the periphery, particularly in the spleen, which is a highly innervated secondary lymphoid organ and a major source of TNF-α during endotoxaemia [28]. Through inhibition of NF-κB nuclear translocation and activation of Jak-STAT pathways, acetylcholine attenuates the production of TNF, IL-1β, IL-6 and IL-18 immune cells expressing the nicotinic acetylcholine receptor subunit α7. In resting conditions, the set point of this reflex arch contributes to establish the magnitude of the innate inflammatory response to acute infection/injury. An additional input required for attenuation of systemic cytokine production is norepinephrine release from splenic nerve endings [28].

In summary, infection or tissue destruction induces the production and release of inflammatory mediators, both at the periphery and in the brain with subsequent activation of the HPA axis and descendent sympathetic and parasympathetic fibres. Cortisol, norepinephrine, other endocrine mediators and acetylcholine regulate the actions of pro-inflammatory cytokines providing a bi-directional interaction between the brain and the immune system at the periphery.

Clinical Correlates of Acute Neuroinflammation

The cognitive and behavioural consequences of impaired immunoregulation have been intensively studied and recent evidence indicates that systemic inflammation translates into acute neuropsychiatric symptoms and acceleration of chronic cognitive impairment.

Animal Studies

Peripheral challenges with bacterial LPS or double-stranded RNA (poly I:C) in animal models have been particularly useful in clarifying the role of systemic inflammation in the emergence of acute neurocognitive and behavioural symptoms. Elevated levels of TNF-α or IL-1 (but not IL-6 or IFN-γ) in the CNS following acute systemic inflammation are responsible for a cluster of transient and stereotyped changes known as 'sickness behaviour'. This syndrome mimics the symptoms experienced by humans during a viral or bacterial infection and manifests with decreased levels of social exploration, locomotor activity and sweetened liquid or food intake [29]. Aged mice show enhanced production of pro-inflammatory cytokines in the brain after LPS stimulation and this translates into a more severe sickness. In contrast, the symptoms are attenuated by IL-10 [30]. Importantly, upregulation of inflammatory mediators such as IL-1, TNF-α, type I interferons and COX-2 in the brain following challenge with systemic LPS have been directly implicated in inducing transient working memory deficits (a proxy of delirium) [31, 32]. The development of acute attentional deficits was associated with pre-existing hippocampal synaptic loss, microglial priming or moderate basal forebrain cholinergic hypofunction [31–33]. All these changes, which leave the brain more susceptible to inflammatory insults, are also known to underlie major predisposing factors of delirium such as increased age and dementia. Furthermore, an increased number of apoptotic cells were observed in the brains of ME7 mice suggesting that the acute neuroinflammatory events not only produce transient symptoms but have long-term irreversible consequences [31, 32]. Multiple neuroanatomical regions and neurochemical changes are likely to be involved in the transduction of inflammatory signals into cognitive, motor and motivational symptoms. Regions known to express IL-1 and TNF-α receptors include the dentate gyrus, hippocampus, anterior pituitary gland, endothelial brain cells, hypothalamus, cortex, nucleus of the solitary tract and ventrolateral medulla [30].

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Human Studies

Elevated levels of plasma C-reactive protein have been reported in patients with delirium in medical or surgical settings [34, 35] but this has not been confirmed by other studies [36–38]. Similarly, reports of higher plasma levels of IL-6, IL-8 and IL-10 in patients with delirium were not consistently replicated. In a case-control study only IL-8 (but not IL-1b, IL-6, IL-10 IL-12p70 and TNF-α) was found to be increased in cerebrospinal fluid of patients with pre- or postoperative delirium [39]. On the other hand, brains of patients who develop delirium near to death show higher microglial and astrocytic activation coupled with increased levels of IL-6 compared with age-matched controls without delirium [40]. Also, one study reported that subjects who developed delirium had a higher ratio of pro-inflammatory to anti-inflammatory cytokines following elective arthroplasty [41]. This suggests that rather than isolated plasma or cerebrospinal fluid levels of cytokines, the combined monitoring of different inflammatory mediators may better capture the complex homeostatic dysfunction occurring during a delirium episode. In the same study, a positive correlation was found between baseline plasma cholinesterase activity and the magnitude of the inflammatory response following surgery in delirium subjects but not in controls [41]. It is possible that plasma cholinesterase activity reflects the inhibitory cholinergic tone at the periphery and that a hyperactive cholinergic anti-inflammatory pathway underlies the greater strength of correlation between plasma cholinesterase activity and the inflammatory response observed in individuals with delirium [41].

Acute systemic inflammation has also been implicated in the pathophysiology of dementia with abundant clinical and neuropathological evidence showing that pre-existing dementia significantly increases the susceptibility of the CNS to the deleterious effects of acute systemic inflammation. In patients with Alzheimer's disease a raised pro-inflammatory cytokine profile over 6 months was associated with an approximately 2-fold increased frequency of neuropsychiatric features characteristic of sickness behaviour. Thus, anxiety and depression were more commonly observed in subjects with elevated serum TNF-α levels while the occurrence of apathy was associated with raised plasma levels of IL-6 [42]. In addition, acute systemic inflammatory events and elevated TNF-α were associated with an increased rate of cognitive decline [43]. It remains to be established to what extent episodes of acute systemic inflammation (i.e. viral or bacterial infection) overlap with episodes of delirium and contribute to the poor cognitive outcome associated with delirium in the long term.

As stated above, there is a bi-directional interaction between acute systemic inflammation and the activation of the HPA axis. Cortisol levels have been found to be elevated in plasma and cerebrospinal fluid of patients with delirium in a diversity of medical and surgical conditions in line with the hypothesis of an 'aberrant stress response' of delirium [44–46]. However, it remains unclear if cortisol elevation is the result of a primary dysfunction of the HPA axis or represents a secondary change to a more intense inflammatory reaction. In any case, increased levels of corticosteroids have a direct negative impact on cognition, including declarative and working memory, which can underlie some features of delirium [47].

Summary and Conclusions

The evidence reviewed so far shows that acute systemic inflammation elicits a prompt neuroinflammatory reaction in the CNS largely mediated by activated microglial cells. The production of pro-inflammatory cytokines including IL-1 and TNF-α induces a cluster of behavioural, cognitive and motivational changes which, in physiological conditions, are necessary to co-ordinate a centralized response to combat potential threats occurring at the periphery. Once homeostasis is regained, the symptoms of sickness resolve and the behaviour returns to normal. However, an unbalanced neuroinflammatory response with exaggerated and prolonged production of pro-inflammatory cytokines can cause more severe neurochemical and functional disturbances affecting neural function and long-lasting structural damage with neuronal cell loss. Even normal levels of acute systemic inflammation can induce such hazardous events when the brain has become more vulnerable due to the effects of aging and/or chronic neurodegeneration. In both conditions, there is a shift towards a pro-inflammatory state in baseline conditions and a dysregulation of homeostatic responses to infection/inflammation. Microglial hyper-responsiveness to acute peripheral inflammation manifests with exacerbated sickness behaviour and working memory deficits in experimental conditions. Thus, it has been proposed that delirium is a maladaptive equivalent to sickness behaviour due to the combined effect of prominent acute neuroinflammation and reduced functional reserve of the brain (fig. 1).

Taken together, the data reviewed here suggests that acute systemic inflammation can have a major impact in the brain and can mediate the relation between increasing age, neurodegeneration and delirium, as well as the rela-

tion between delirium and cognitive deterioration in the long term. Full understanding of these pathophysiological mechanisms would be crucial to develop sensitive and specific biomarkers monitoring the progression of changes underlying delirium. Indeed, there is a compelling need to predict the risk of delirium and further cognitive decline in subjects with dementia exposed to acute inflammation. In a typical acute medical ward there may be dozens of patients infected with bacteria, but the magnitude of the innate immune responses will vary considerably, spanning from having no observable inflammation to the release of pro-inflammatory cytokines that mediate tissue injury and delirium. However, the evidence relating inflammation to delirium is difficult to translate into clinical practice as the relationship between the absolute levels of serum inflammatory mediators and clinical symptoms is inconsistent. Future studies are also needed to address the possibility that dysfunctional neural circuits affected by the on-going neurodegenerative process could alter systemic innate immune responses. Similarly, there is a lack of studies analysing the interconnection between the innate immune response and brain-to-immune pathways in subjects before, during and after delirium. Finally, the progressive understanding of the interaction between the brain and peripheral organs could lead to the development of new therapeutic agents [48].

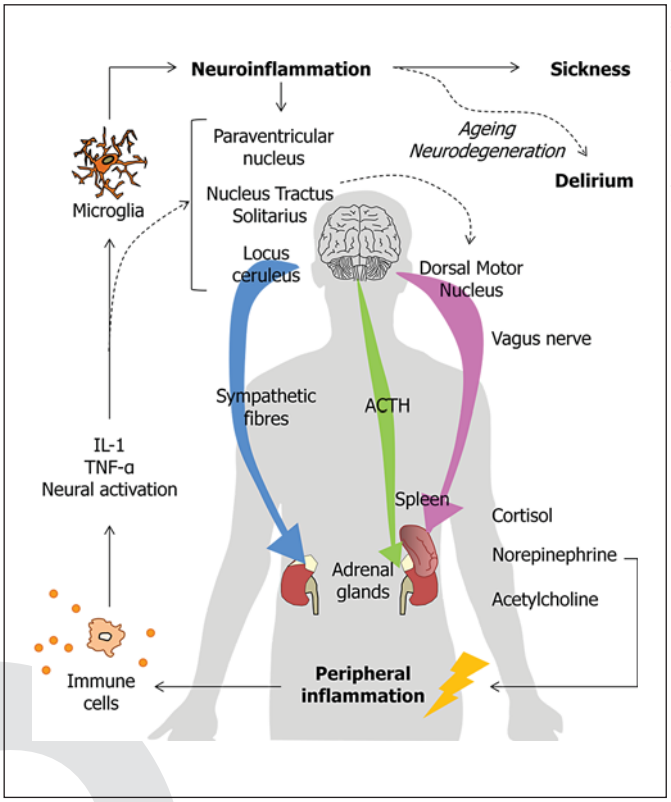

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Fig. 1. Pathophysiological pathways potentially implicated in the relationship between delirium and inflammation.

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