Neuroscience and Biobehavioral Reviews 37 (2013) 1–10

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Cytokines: How important are they in mediating sickness?

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ARTICLE INFO

Article history:
Received 11 June 2012
Received in revised form
28 September 2012
Accepted 4 November 2012

Keywords:
Cytokines
Sickness
Systemic inflammation
Delirium

ABSTRACT

Sickness refers to a set of coordinated physiological and behavioral changes in response to systemic inflammation. It is characterized by fever, malaise, social withdrawal, fatigue, and anorexia. While these responses collectively represent a protective mechanism against infection and injury, increasing lines of evidence indicate that over-exaggerated or persistent sickness can damage the brain, and could possibly raise the risk to developing delirium. Therefore, a clear understanding in sickness will be beneficial. It has long been believed that sickness results from increased systemic cytokines occurring during systemic inflammation. However, in recent years more and more conflicting data have suggested that development of sickness following peripheral immune challenge could be independent of cytokines. Hence, it is confusing as to whether cytokines really do act as primary mediators of sickness, or if they are secondary to alternative inducing factor(s). In this review, we will (1) introduce the relationships between systemic inflammation, cytokines, sickness, and delirium, and (2) attempt to interpret the recent controversies.

Contents

1. Introduction

We all prefer to live healthily and to be free of sickness. Getting sick because of infection (Campisi et al., 2003; Dantzer et al., 2008; Hart, 1988) or injury (Liu et al., 2008; Swain and Le, 1998) is discomforting and interferes greatly on our daily lives. While sickness was traditionally thought as a malfunction due to systemic inflammatory events, it is in fact an adaptive mechanism to facilitate recovery. This is mediated by a series of highly coordinated physiological and behavioral changes, including fever, pain, fatigue, cognitive loss, anorexia, anhedonia, and social withdrawal (Dantzer, 2009; Dantzer et al., 2008; Hart, 1988), which will be collectively referred to as sickness or sickness responses throughout this review. There is now ample evidence to show that these alterations can indeed help to fight infection (Hart, 1988). For example, an elevation in body temperature during fever is not only unfavorable to the growth of some pathogens, but also stimulates the activation and proliferation of immune cells. A reduction of appetite leads to a lowered intake of iron, which is important for the growth and replication of many pathogens. Nevertheless, while these responses are useful if well controlled, over-exaggerated sickness can be damaging. For instance, a persistent increase of brain temperature during fever might enhance neuronal excitotoxicity (Suehiro et al., 1999) and lead to abnormalities of blood–brain-barrier permeability (Sharma and Hoopes, 2003). A lowered food intake and greater thermogenesis would cause weight loss in a long run. Moreover, there is now evidence to suggest that dysregulated sickness responses, together with other risk factors such as aging and pre-existing dementia, could lead

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0149-7634/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neubiorev.2012.11.001

to delirium (de Rooij et al., 2007; Holmes et al., 2011). Hence, it will be advantageous if we can understand the mechanisms of how sickness develops, and to implement suitable approaches to maximize their benefits without causing severe side effects.

Given that individual symptoms of sickness may be regulated by specific neuronal networks, and that they are natural responses to systemic inflammation, it is reasonable to think that there are some biological signals relating the inflammatory events occurring at the periphery to the brain for inducing sickness responses. Over the last two decades, cytokines have emerged to be these linking signals. Accordingly, systemic inflammation triggers drastic releases of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, all of which can act on the brain, despite the blood–brain-barrier (BBB), and lead to sickness. A number of neural and humoral routes are involved. However, an increasing number of reports have shown that under some occasions, sickness following peripheral immune challenge could be independent of central and peripheral cytokine increases (Blatteis, 2007; Campisi et al., 2003; Murray et al., 2011; Teeling et al., 2010, 2007). Therefore, we question the importance of cytokines, arising both systemically and within the brain, as mediators of sickness. Can the induction of cytokines alone be sufficient to cause sickness? Or are they simply secondary to alternative triggers of sickness? Moreover, what are the roles of anti-inflammatory cytokines in sickness?

Here, we summarize the relationships between systemic inflammation, cytokines, and sickness. Based on this background, we try to interpret the emerging controversial issues, and point out the gaps of knowledge. Moreover, since delirium may result from over-exaggerated sickness (de Rooij et al., 2007; Holmes et al., 2011), we will also try to suggest possible roles of cytokines in delirium.

2. Cytokines are induced centrally and peripherally during systemic inflammation

Inflammation describes a cascade of vascular changes (e.g. vasodilation and increased capillary permeability) and cellular changes (e.g. recruitment and activation of immune cells) in response to infection and tissue injury. These physiological responses are orchestrated by increased levels of cytokines produced mainly by activated immune cells at the site of inflammation. Once produced, cytokines act both locally in autocrine and paracrine manners, and systemically at distant organs (Dantzer, 2009; Kelso, 1998). For example, IFN-γ stimulates tissue macrophages to up-regulate inducible nitric oxide synthase (iNOS) expression, leading to nitric oxide release (Blanchette et al., 2003). Nitric oxide in turn exerts antimicrobial (Mehta et al., 2012) and vasodilatory effects (Engelberger et al., 2011) in the microenvironment. Systemically, IL-6 produced at the inflammatory site is circulated to the liver, where it synergistically acts with IL-1β produced by Kupffer cells to trigger release of serum amyloid-A, which is involved in the complement cascade (Betts et al., 1993). Yet, if we take a step further, we should ask an important question: How do immune cells sense invading pathogens and injured tissues and mount the cytokine responses for inflammation?

In respect to systemic infection, this is accomplished via the interactions between pathogen-associated molecular patterns (PAMPs) and pathogen recognition receptors (PRRs) (Bianchi, 2007; Kawai and Akira, 2009; Lee and Kim, 2007). PAMPs are conserved molecular motifs present in pathogens but are absent in the host, and can thus be distinguished as non-self by the immune system. PRRs are membrane bound or secretory receptors specific for these PAMPs, and they are expressed by many immune cell types such as monocytes/macrophages, natural killer cells, neutrophils, and dendritic cells. Binding of a PAMP to the corresponding PRR activates classical NF-κB, MAPK, and IRF3 signaling pathways, leading to increased expression of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and interferons (Kawai and Akira, 2009). Today, several classes of PRRs have been identified, including the Toll-like receptors (TLRs) (Hedayat et al., 2011; Kawai and Akira, 2008), the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (Saleh, 2011), the retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) (Kawai and Akira, 2008; Liu and Gu, 2011), and the C-type lectin receptors (CLRs) (Osorio and Reis e Sousa, 2011). For instance, lipopolysaccharide (LPS), which is a component of the outer membrane of gram negative bacteria and a commonly used immunostimulant, is a ligand for TLR4 to activate NF-κB (Medvedev et al., 2007).

Although tissue injury is often associated with a pathogenic stimulus, i.e. when one cuts his finger and exposes the underlying tissues to the limitless bacteria and viruses in the environment, injury alone can also trigger inflammation, a process known as "sterile inflammation" (Chen and Nunez, 2010). An illustration of this is that shortly after a person puts his finger on a hot stove, swelling and redness develop at the contact site. The mechanisms by which injury induces inflammation are less clear. It is believed that necrotic cells release endogenous danger signals known as alarmins, which act on innate immune cells to activate similar receptors (e.g. TLRs) and signaling pathways (e.g. NF-κB pathway) to those used by PPRs/PAMPs, leading to cytokine production (Bianchi, 2007; Rosin and Okusa, 2011). For example, high mobility group box 1 (HMGB1), a nuclear protein which facilitates DNA bending, is released by necrotic cells and signals through TLR2 and TLR4 to activate NF-κB dependent transcription (Park et al., 2006).

Systemic inflammation not only induces cytokines systemically, but also within the brain. A good example is that systemic LPS challenge causes the brain endothelium (Quan et al., 1998; Singh and Jiang, 2004) and macrophage-like cells (Buttini et al., 1996; Eriksson et al., 2000; van Dam et al., 1992) to produce IL-1, which can diffuse to the brain parenchyma (Vitkovic et al., 2000). Therefore, the brain can respond to PAMPs and alter its own cytokine profile.

In addition to the generation of cytokines to trigger inflammation, infections and injuries can induce sickness. This leads us to the next step: Do cytokines regulate the development of sickness?

3. The discovery of cytokines as mediators of sickness

Following the development of recombinant cytokines in the 1980s, it was observed that patients and animals given an exogenous source of cytokines often developed flu-like symptoms and neuropsychiatric complications. For example, in a group of gastrointestinal cancer patients, intravenous injection of recombinant IL-1β resulted in fever, headache, rigors, nausea, and vomiting (Crown et al., 1991). Moreover, around 20% of patients receiving long term IFN-α therapy for viral hepatitis displayed neuropsychiatric symptoms like depression and altered consciousness (Renault et al., 1987). In animals, administration of IL-1β and TNF-α lead to a wide range of sickness responses, including fever, suppressed feeding, social withdrawal, immobility, and weight loss (Bluthe et al., 2000a; Dantzer et al., 2008; Kent et al., 1992; Palin et al., 2008; Stefferl et al., 1996). In contrast, injection of IL-6 alone into the brain induces a partial spectrum of sickness only, i.e. fever and reduced voluntary activity, but it could act synergistically with a sub-threshold dose of IL-1β to trigger anorexia and weight loss (Harden et al., 2008). Interestingly, similar sickness responses were observed when animals were given either central or systemic injections of bacterial LPS, which is an inducer of cytokines including IL-1β, IL-6, and TNF-α in the brain and systemically (Bluthe et al., 1992; Henry et al., 2008; Huang et al., 2008). Taken together, these findings were suggestive for the idea that sickness induced by LPS

resulted from increased systemic cytokines. However, this was not initially accepted because of the enormously high doses of cytokines used in the respective studies.

To confirm the effect of endogenous cytokines in mediating sickness, experiments were done to verify whether deficiency of a single cytokine or its actions would blunt sickness responses to LPS. The involvement of endogenous IL-1 is quite clear, because both systemic (Bluthe et al., 1992) and central (Laye et al., 2000) injections of IL-1 receptor antagonist (IL-1Ra) abrogated the suppressive effects of intraperitoneally injected LPS on social and/or feeding behaviors. Likewise, when compared to wild-type mice, IL-6 deficient mice exhibited less responsiveness to intraperitoneally and intracerebroventricularly injected LPS and IL-1β (Bluthe et al., 2000b), and in wild-type rats a pre-treatment with anti-IL-6 antibody abolished the effects of subcutaneously injected LPS on fever, voluntary running and food intake (Harden et al., 2006). More importantly, by blocking the actions of TNF-α within the brain via an intracerebroventricular injection of a fragment of the TNF soluble receptor, IL-1RI deficient mice developed less severe sickness responses toward intraperitoneal injection of LPS (Bluthe et al., 2000a). This indicated that under physiological conditions, cytokines do not work independently, but rather functionally interact with each other in the form of cytokine networks to trigger different symptoms of sickness (Dantzer, 2009).

Whereas pro-inflammatory cytokines participate in causing sickness, anti-inflammatory cytokines resolve sickness, such as when pathogens have been eliminated by systemic inflammatory processes. For instance, IL-10 is a well known anti-inflammatory cytokine which suppresses the synthesis of pro-inflammatory cytokines, e.g. IL-1β, IL-6, and TNF-α (Glocker et al., 2011). Wild type mice intraperitoneally injected with recombinant IL-10 before LPS challenge showed attenuated febrile responses as compared to mice treated with LPS only (Leon et al., 1999). In the same study, it was shown that following an intraperitoneal injection of LPS, IL-10 knockout mice developed exacerbated fever, further depressed feeding, and increased weight loss as compared to their wild-type counterparts. In another study, IL-10 knockout mice displayed greater cognitive deficits and immobility in response to intraperitoneally injected LPS (Richwine et al., 2009).

Thus, cytokines arising from inside and outside the brain modulate sickness. For cytokines arising systemically, they should signal back to the brain to take effects. However, since cytokines are hydrophilic molecules, they cannot freely pass through the BBB to enter the brain (Chang et al., 2009). This leads us to the next question: How do systemic cytokines affect the brain in the presence of the BBB?

4. Systemic cytokines act on the brain via multiple routes

There are many routes by which systemic cytokines act on the brain, and they can be grossly classified into either being humoral dependent or neural dependent. Regarding the major humoral pathways, circulating cytokines can activate macrophage-like cells lining the circumventricular organs (CVO) (Dantzer, 2001, 2009; Dantzer et al., 2008; Schiltz and Sawchenko, 2002). These are brain regions that lack a functional BBB, including the median eminence (ME), organum vasculosum of the lamina terminalis (OVLT), area postrema (AP), and the suprafornical organ (SFO). Upon activation, these macrophage-like cells locally secrete high levels of cytokines, which can then enter the brain by volume diffusion (Vitkovic et al., 2000). Furthermore, increasing lines of evidence indicate that certain cytokines such as IL-1 (Banks et al., 2001, 1991), IL-1Ra (Gutierrez et al., 1994), TNF (Osburg et al., 2002), and IL-6 (Banks et al., 1994) can be selectively transported across the BBB in a blood-to-brain direction, mostly via saturable transport mechanisms. Circulating cytokines may also act on the brain vascular endothelium to trigger release of cytokines (An et al., 2011; Fabry et al., 1993; Thornton et al., 2010) and prostaglandin E2 (PGE_2) (Cao et al., 2001, 1996; Konsman et al., 2004). The latter binds to neuronal PGE_2 receptor 3 (EP3) and 4 (EP4) in the brainstem and hypothalamus, and regulates hypothalamic–pituitary–adrenal (HPA) axis activation and fever (Lazarus, 2006).

Evidence for the involvement of neural pathways in cytokine-mediated sickness was based on several major findings. To begin with, c-Fos is an immediate early gene and its expression has been commonly used as a marker of neuronal activation. An intraperitoneal injection of LPS, which potently stimulates cytokine production, leads to increased c-Fos immunopositive neurons at the primary, e.g. the nucleus tractus solitarius (NTS) and secondary projection areas, e.g. the supraoptic nucleus (SON) and paraventricular hypothalamic nucleus (PVH) of the vagus nerve (Dantzer, 2001; Dantzer et al., 2008). As the vagus nerve represents the major afferent pathway from the abdominal region to the brain, subdiaphragmatic vagotomy experiments were performed to see if this would reduce LPS-induced c-Fos expression. As expected, subdiaphragmatic vagotomy not only blocked LPS-induced brain c-Fos upregulation (Konsman et al., 2000; Wan et al., 1994), but also abolished LPS-induced brain IL-1 mRNA at the hippocampus and hypothalamus (Laye et al., 1995) and the decrease in social behavior (Bluthe et al., 1994; Konsman et al., 2000). Similarly, subdiaphragmatic vagotomy reduced social withdrawal and brain IL-1β mRNA expression following intraperitoneal IL-1β challenge (Hansen et al., 1998). Later, it was shown that an intraperitoneal LPS challenge up-regulated IL-1β immunoreactivity in immune cells associated with the abdominal vagus nerve (Goehler et al., 1999), vagus nerve sensory neurons express IL-1RI and intravenously injected IL-1β could stimulate vagus sensory activity (Ek et al., 1998), and that electrical stimulation of the vagus nerve elevated both brain IL-1β mRNA and protein levels and activated the HPA axis (Hosoi et al., 2000). Taken together, it would be reasonable to deduce that inflammation increases levels of IL-1β, which then stimulates the vagus nerve to fire electrical signals back to the brain. These signals in turn up-regulate brain IL-1β expression, and could possibly modulate specific neuronal networks that control social behavior. However, subdiaphragmatic vagotomy did not reverse social withdrawal when IL-1β was injected via other administrative routes (Bluthe et al., 1996a,b). This indicated that the vagus nerve is likely to be only responsible for triggering sickness responses when inflammation takes place at the abdominal region but not at other peripheral sites.

The presence of both humoral dependent and neural dependent routes implies that the onset of sickness is regulated by several routes, and that individual symptoms of sickness can be differentially regulated by separate routes. For example, subdiaphragmatic vagotomy blocked fever in response to low doses of LPS (Romanovsky et al., 1997) or IL-1β (Hansen et al., 2001), but not to high doses. In contrast, vagotomy was sufficient to inhibit social withdrawal (Konsman et al., 2000) even to high doses of LPS or IL-1β, and the reduction in sweetened milk consumption, food intake, and locomotor activity triggered by a high dose of IL-1β (Wieczorek et al., 2005). These studies imply that although the vagus nerve represents the major periphery-CNS pathway responsible for fever towards low quantities of intraperitoneally injected LPS or IL-1β, its role in fever is masked when high levels of LPS and cytokines are present to affect the brain via the humoral routes. On the other hand, the vagus nerve is certainly important for behavioral depression, even under high quantities of circulating LPS or IL-1β. Also, it is obvious that cytokine messages can be conveyed more quickly to the brain through the neural dependent routes than through the humoral dependent routes. As suggested by Dantzer, systemic inflammation may first activate the fast neural routes,

which sensitizes the brain to the subsequent actions from the slow humoral routes (Dantzer, 2001, 2009).

5. Cytokine-induced sickness: can we extend our perspectives to look at cytokines in delirium?

As discussed, sickness is an adaptive strategy aimed to improve survival and recovery from systemic inflammatory insults, involving activation of the innate immune system to produce cytokines and stimulation of specific neuronal networks to elicit a set of physiological (i.e. fever) and behavioral (i.e. anorexia, social withdrawal, immobility, and fatigue) responses. However, when these responses become dysregulated, the strategy fails and causes harm instead. For instance, a high fever might lead to excitotoxicity (Suehiro et al., 1999) and BBB abnormalities (Sharma and Hoopes, 2003). Likewise, in recent years there is growing evidence to suggest that an exaggerated or dysregulated sickness could result in delirium (Cunningham and Maclullich, 2012; Munster et al., 2011; Murray et al., 2012). If this is the case, it is expectable that cytokines, which mediate sickness, should also regulate delirium.

Delirium, also commonly referred to as acute confusional state, is characterized by inattention, altered consciousness, cognitive deficits, hallucinations, and disorientation (Dasgupta and Hillier, 2010). It is estimated that delirium affects as much as a quarter of general hospitalized patients. More importantly, delirium is strongly associated with prolonged hospitalization time and costs, greater subsequent cognitive decline, and increased mortality (Fong et al., 2009).

Now how does delirium relate to exacerbated sickness responses? The answer lies in that both entities could be initiated or precipitated by systemic inflammation, and they exhibit severe and overlapping cognitive dysfunctions. In young and healthy individuals (Grigoleit et al., 2011, 2010; Reichenberg et al., 2001) and rodents (Barrientos et al., 2006; Tarr et al., 2011), a moderate degree of systemic inflammation leads no or mild cognitive deficits, on top of classical symptoms of sickness, e.g. fever, and immobility. Nevertheless, under severe systemic inflammation, as in the case of sepsis, humans can suffer from delirium, unconsciousness, and long-term cognitive decline post-recovery (Iwashyna et al., 2010). Although it is difficult to assess delirium in animals, rats that have undergone cecal ligation and puncture, i.e. a model for sepsis caused by peritonitis due to release of gut microflora, showed marked learning impairments in the passive avoidance task (Shimizu et al., 1999). Moreover, an introduction of septic shock doses of LPS led to significantly poorer working memory performance in the radial arm maze even after 3 months post-injection, and this was associated with neuronal apoptosis and reduced cholinergic innervation (Semmler et al., 2007). In the same study, reduction in open-field exploratory activity persisted for 3 months post-sepsis, whereas it usually restores within a day in young and healthy rodents after subseptic levels of LPS (Cunningham et al., 2009). Therefore, as the level of systemic inflammation increases, so does the severity of sickness responses, such as having a prolonged reduction in open-field activity. Moreover, while cognitive impairments are absent or mild under low to moderate grade of systemic inflammation, they become prominent during high grade systemic inflammation. These impairments resemble those observed in delirious patients, suggesting that exaggerated sickness can manifest as delirium.

Yet, the picture is not that simple. Numerous epidemiological studies have indicated that aging and dementia, particularly Alzheimer's disease, as major risk factors for delirium (Fong et al., 2009; Holmes et al., 2011) Thus, while a moderate level of systemic inflammation causes adaptive sickness responses in young and healthy individuals without delirium, the same grade of systemic inflammation can precipitate delirium in aged and/or dementia patients. Based on this observation, the immediate question we should ask is what differences between a "young and healthy brain" and an "aged and demented brain" are responsible for raising the susceptibility to delirium? The postmortem brains of delirious patients were associated with increased microglial and astrocytic immunoreactivities when compared to the brains of non-delirious patients, giving the notion that neuroinflammation participates in delirium (Munster et al., 2011). In a similar fashion, both aging and ongoing neurodegeneration, especially in Alzheimer's disease, can "prime" microglia to systemic inflammation (Perry, 2010). That is to say, in the absence of immune challenge, primed microglia appear to be morphologically activated but they do not express IL-1β. However, during systemic inflammation primed microglia will produce much more IL-1β. It is believed that this kind of priming results from loss of interactions between CD200 on neurons and CD200 receptors on microglia, which occurs during neuronal death in chronic neurodegenerative disorders (Walker et al., 2009). Until recently, ME7 prion-diseased mice have been proposed to be a suitable animal model of delirium during dementia (Murray et al., 2012). These mice were inoculated with the ME7 strain of prion to induce neurodegeneration for 12 weeks, leading to progressive priming of microglia and synaptic loss. In humans, both processes proceed gradually during normal aging and Alzheimer's disease (Hatanpaa et al., 1999; Heinonen et al., 1995; Perry, 2010), and might account for the higher vulnerabilities toward delirium of these populations. Following systemic LPS challenge, ME7 mice displayed acute working memory deficits in the T-maze, i.e. they were less able to attend to the arm that they had visited 25 s earlier. This behavior is analogous to that observed in delirium, in which patients are frequently unable to maintain attention for more than 30 s (Hart et al., 1997). Taken together, ME7 mice represent an excellent model to study delirium in patients with dementia. Upon systemic inflammation induced by LPS (Cunningham et al., 2009) or the synthetic double-stranded RNA poly I:C (Field et al., 2010), ME7 mice displayed exaggerated sickness responses and up-regulated expression of inflammatory mediators such as IL-1β, TNF-α, IL-6, type I interferons, and COX-2 in the brain, supporting the idea that enhanced neuroinflammation could be involved in the increased risk of dementia patients to develop delirium following systemic inflammation. More importantly, both LPS (Cunningham et al., 2005) and poly I:C (Field et al., 2010) resulted in greater number of apoptotic cells in the brains of ME7 mice, which not only may account for the exacerbated sickness responses and memory deficits in these mice, but also the faster rate of cognitive decline after delirium.

It is now clear that aging and dementia (e.g. Alzheimer's disease) can increase the chance of an individual to develop delirium under acute systemic inflammation. Nevertheless, aging (Wei et al., 1992) and dementia (Mancinella et al., 2009) are also associated with chronic low grade inflammation. This makes us ponder: Can chronic low grade inflammation act as a predisposing factor to delirium? Unfortunately, this direction has not been thoroughly addressed in the field. There is evidence to show that obesity (Moroz et al., 2008; Yi et al., 2012), diabetes (Luo et al., 2002; Moroz et al., 2008), and alcohol abuse (Zhao et al., 2013) can cause activation of microglia and astrocytes. Whether such activated microglia behave similarly to the primed microglia in the ME7 model to release much more inflammatory mediators upon acute systemic inflammation is unclear. Recently, experimental results from our group have demonstrated that chronic cigarette smoke exposure can affect the synapse and cytoskeleton, characterized by decrements in presynaptic proteins synaptophysin and synapsin-I, reduced tubulin acetylation, and up-regulation of tau phosphorylation (Ho et al., 2012), all of which are pathophysiologies found in Alzheimer's disease. Interestingly, obesity, diabetes, alcohol abuse, and long-term smoking can all increase risks to Alzheimer's disease

(Businaro et al., 2012; Giunta et al., 2012; Holscher, 2011; Tyas, 2001), which we emphasize is also a major risk factor of delirium (Holmes et al., 2011; Perry, 2010). Despite having complex and diverse physiologies, all four conditions involve chronic low grade systemic inflammation, and may possibly prime the brain to trigger delirium.

So how do cytokines fit in to the precipitation of delirium by systemic inflammation? Unfortunately, prior research in this area is quite limited. Given that we have discussed how cytokines mediate sickness, and that delirium could be a manifestation of exacerbated sickness responses, we hope that the participation of cytokines in delirium should be appealing. Further evidence comes from the above studies showing that acute deficits of working memory in LPS-challenged ME7 mice were accompanied by increased expression of brain cytokines (Cunningham et al., 2009; Murray et al., 2012), and most of these cytokines are known to modulate mood and cognition (Dantzer, 2001, 2009; Dantzer et al., 2008). Moreover, similar to the observation of increased cytokines during sickness, cytokines are also elevated in delirious patients as compared to non-delirious patients, particularly blood IL-6 and IL-8 (de Rooij et al., 2007; van Munster et al., 2010, 2008), CSF IL-8 (Hall et al., 2011), and brain IL-6 immunoreactivity (Munster et al., 2011). In addition, long-term IFN-α therapy for chronic viral hepatitis has been attributed to delirium in up to one fifth of the patients (Renault et al., 1987). Lastly, delirium is associated with cholinergic hypofunction (Flacker and Lipsitz, 1999), and use of anticholinergics can increase severity of delirium in elderly patients (Han et al., 2001). Of relevance to this is that IL-1 suppresses cholinergic pathways (Li et al., 2000).

To date, the links between cytokines and systemic inflammation-precipitated delirium is in fact still at its infancy. The urgent question we should ask is how we could extend our knowledge from cytokine-induced sickness to the relationships between cytokines and delirium, as summarized in Fig. 1, and if this could provide insights on the prevention, treatment, and evaluation of recovery for delirium. For example, if cytokines are important to delirium, which cytokines can be biomarkers to predict whether a patient is likely to develop delirium, and which cytokines can be used to evaluate recovery of patients after delirium? It has been reported that peak levels of blood IL-8 and IL-6 occur before and during delirium, respectively, in elderly patients with hip fractures (van Munster et al., 2010, 2008). Furthermore, low insulin-like growth factor 1 (IGF-1) and high initial IFN-γ levels in blood are correlated with the incidence and recovery of delirium, respectively (Adamis et al., 2007). Table 1 summarizes the available literature showing relevance of cytokines to delirium. In future, more cross-sectional analyses should be performed to verify whether these cytokines are also associated with delirium under other causes of systemic inflammation. Once such correlations are established, the next step will be to test, using animal models, whether cytokines do regulate delirium, or if they are merely bystanders. This will require careful validation on how delirium can be successfully induced in animals, and which behavior test(s) would be the most appropriate to assess delirium. On the other hand, since dexamethasone could not reduce LPS-triggered sickness despite blocking increases of blood cytokines (Murray et al., 2011; Teeling et al., 2010), targeting circulating cytokines levels is probably ineffective against delirium, although data on manipulation of other key cytokines such as IL-8 is still missing.

In the next section, we highlight several interesting examples in which cytokines may appear to be disconnected to sickness development. Our purpose is not to against the model of cytokine-induced sickness. Instead, we would like to stimulate our readers to not only redefine the importance of cytokines in mediating sickness, but also on top of that to explore the significance of cytokines in delirium.

6. Cytokines: to what extent can they explain systemic inflammation-induced sickness?

In previous sections, we have provided multiple lines of evidence to support the model of cytokine-induced sickness. Firstly, systemic inflammation, induced either by infection or tissue injury, results in heightened levels of cytokines in the brain and at the periphery. Secondly, both exogenously administered and endogenously produced cytokines are involved in the induction of sickness responses, e.g. fever, social withdrawal, suppressed feeding. Thirdly, systemic cytokines communicate with the brain through a number of fast neural and slow humoral routes to trigger neuronal activation, increased expression of mRNA for brain cytokines, and production of PGE_2. Despite all these evidence, the big question we should ask is how important cytokines are as mediators of sickness.

In order to answer this question, it would be easier if we first think about it from another perspective: Can we get sick without the effects of cytokines? Interestingly, some cytokine-induced sickness responses share high similarity with the physiological and behavior changes triggered by necrotic drugs, in the absence of systemic inflammatory insults. For example, the use of amphetamine and its analogues causes fever (Levi et al., 2012), and apomorphine reduces appetite (Duterte-Boucher et al., 1989). In these scenarios, cytokines are unlikely to be the major players because we do not observe drastic elevations of cytokines. Instead, the appearance of fever and reduced feeding is more related to the modulation of neurotransmitters such as serotonin, epinephrine, and dopamine in the brain by the drugs above. Hence, we can feel sick without any effects from cytokines. Yet, does this apply to the adaptive sickness responses towards systemic inflammation, which certainly involves increased cytokines? In this aspect, recently many studies have suggested that sickness could possibly be developed without the aid of peripheral and/or central cytokines (Blatteis, 2007; Campisi et al., 2003; Murray et al., 2011; Teeling et al., 2010, 2007; Zhang et al., 2008). These surprising findings have enlightened us to rethink about the current model of cytokine-induced sickness, and led us to share our opinions on the importance of cytokines in mediating sickness in this review.

While most studies have reported that elevations of cytokines in the brain and/or blood occur before the onset of sickness responses, this is not mandatory in all cases. In one study, following an intravenous injection of LPS, the body temperature started to rise within 10 min (Sehic et al., 1996a,b), while the first cytokine to increase in the plasma, i.e. TNF-α, was not detected within 30 min (Jansky et al., 1995). Here, the induction of plasma TNF-α after 30 min is not surprising because cytokines are normally not constitutive in immune cells and their synthesis are primarily regulated by transcriptional control. However, the quick hyperthermic response beginning in several minutes clearly demonstrated that fever should have been initiated by another mechanism. In this regard, Blatteis et al. have proposed that fever after an intravenous injection of LPS is biphasic, characterized by a rapid onset, PGE_2-independent initial phase, and a COX-2/PGE_2-dependent late phase (Blatteis, 2007). Intravenously injected LPS activates the complement system to produce the anaphylatoxin C5a, which signals Kupffer cells in the liver to almost instantly release PGE_2. PGE_2 binds to and activates vagal afferents, transmitting signals back to the NTS, and from there, via the central noradrenergic bundle, to the ventromedial preoptic area (VMPO) to trigger local production of norepinephrine (NE). NE in turn acts on neuronal α_1-adrenergic receptors and glial α_2-adrenergic receptors to induce the early and late phases of fever, respectively. Since plasma cytokines increased after the early phase of fever, they were not involved in initiating fever, but they could still contribute to the late phase of fever directly by entering the brain to act on the required neuronal networks, and/or indirectly by stimulating brain

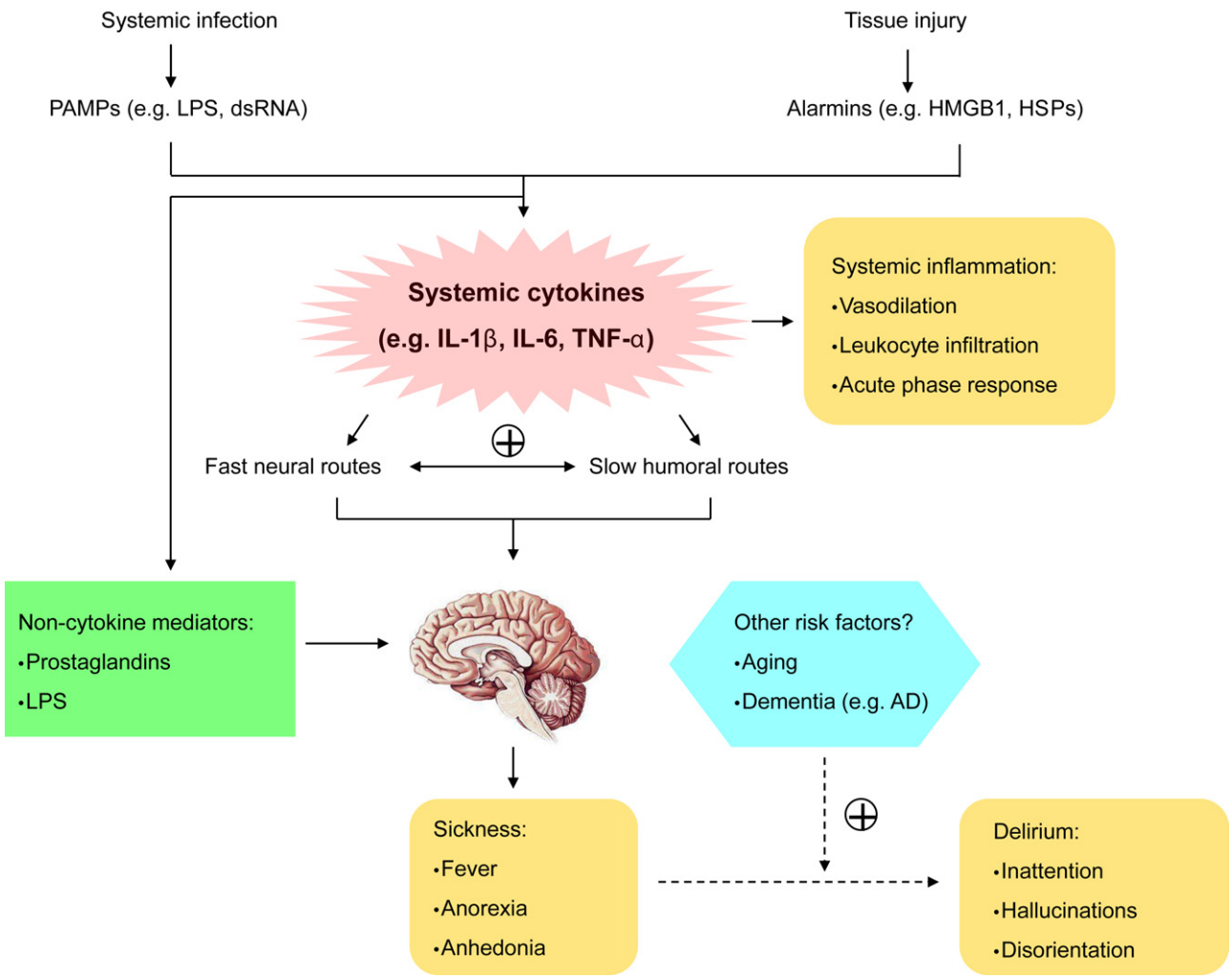

Fig. 1. Summary diagram illustrating the relationships between systemic inflammation, cytokines, sickness, and delirium. Starting from the top, systemic infection and tissue injury, respectively, give rise to pathogen-associated molecular patterns (PAMPs) and alarmins, which both act on innate immune cells to trigger production of cytokines such as IL-1β, IL-6, TNF-α. These cytokines not only orchestrate local and distant inflammatory changes, but can also communicate with the brain via the fast neural and the slow humoral routes to induce sickness. It is believed that activation of the fast neural routes sensitizes the brain to the effects of the slow humoral routes, thereby amplifying sickness responses. Alternatively, infections and/or injury can generate non-cytokine mediators of sickness, including circulating prostaglandin E2 and LPS, which can both directly take effects at the brain and cause sickness. Although sickness is an adaptive response to facilitate recovery, in extreme cases it may manifest as delirium if uncontrolled. In young and healthy individuals, elevated cytokine levels by systemic inflammatory events lead to sickness. However, in the presence of other risk factors such as having an old age and/or dementia (e.g. Alzheimer's disease, AD), the same cytokines increases could possibly precipitate delirium. *Abbreviations*: LPS, lipopolysaccharide; dsRNA, double stranded RNA; HMGB1, high mobility group box 1; HSPs, heat shock proteins.

endothelial and perivascular microglia to produce the fever mediator PGE_2. On the other hand, a subcutaneous injection of *E. coli* in rats caused fever and reduced activity starting from the fourth hour, before the increases of cytokines in the brain and plasma beginning at the sixth hour, and initial rise of circulating endotoxins at the eighteenth hour (Campisi et al., 2003). Therefore, in this study brain and blood-borne cytokines and circulating endotoxins came after the onset of sickness, and they could not have initiated sickness. However, the authors did find increased local cytokine synthesis at the injection site as early as second hour. Hence, prior to spilling over to the bloodstream to affect the brain via the humoral route, these locally produced cytokines could have directly activated neighboring nerve terminals of afferent nerves, immediately transmitting signals back to the brain to stimulate the neuronal networks controlling fever and activity, before brain cytokines were up-regulated. Although the actual identity of the nerve(s) responsible for communicating subcutaneous inflammatory signals back to the brain have not been determined, the vagus (Bluthe et al., 1996a,b) and the glossopharyngeal nerves (Romeo et al., 2001) are responsible for communicating inflammatory stimulus from the abdominal and oral cavities to the brain, respectively, suggesting that functional neuronal circuitries should exist to relay skin inflammation to the brain. Furthermore, even though blood-borne cytokines were not required for initiating sickness, activation of the fast neural routes may sensitize the brain to the effects of the slow humoral routes (Dantzer, 2001, 2009). Importantly, since in the second study fever and reduced activity persisted as long as brain and plasma cytokines were still elevated, cytokines were still likely to be required to sustain sickness responses during an infection. Therefore, it should be noted that the induction of circulating and brain cytokines do not necessarily have to occur before the onset of sickness responses, even though cytokines do mediate sickness.

Another striking observation is that sickness responses can be effectively reduced without suppressing central and/or peripheral cytokine levels. In studies performed by Teeling et al., pretreatment of mice with indomethacin, which is a non-selective COX inhibitor and inhibits prostaglandins production, abrogated the depressive effect of an intraperitoneal injection of a subpyrogenic dose of LPS on burrowing activity (Teeling et al., 2007). Likewise, in another study pretreatment of mice with a selective COX-1

Table 1
A summary of the available studies in the literature showing relevance of cytokines to delirium.

Cytokine(s)	Reference(s)	Major findings
IFN-α	Renault et al. (1987)	Delirium in patients undergoing IFN-α therapy for chronic viral hepatitis
IL-6	Plaschke et al. (2010)	Higher blood IL-6 in delirious versus non-delirious patients after open-heart cardiac surgery
	Munster et al. (2011)	Higher IL-6 immunoreactivity in postmortem brains of delirious than in non-delirious patients
	Katsumata et al. (2007)	IL-6 was higher in the CSF of delirious than in non-delirious patients with systemic lupus erythematosus
IL-8	Hall et al. (2011)	Elevated IL-8 in the CSF of patients with delirium versus those without delirium
IGF-1	Wilson et al. (2005)	Low circulating IGF-I is a risk factor for delirium
IL-6, IL-8	van Munster et al. (2010), van Munster et al. (2008)	Higher blood IL-6 and IL-8 levels in delirious than in non-delirious elderly patients with hip fracture. The highest levels of IL-6 and IL-8 were observed during and before delirium, respectively. Patients with hyperactive and mixed subtypes of delirium had higher IL-6 than those with hypoactive delirium
IGF-I, IFN-γ	Adamis et al. (2007)	Low IGF-I and high initial IFN-γ in blood are associated with the incidence and recovery of delirium, respectively
IGF-I, IL-1RA,IFN-γ	Adamis et al. (2009)	Low blood IGF-I and IL-1RA levels are correlated with the incidence of delirium. Low IGF-I and high IFN-γ are associated with more severe delirium

inhibitor piroxicam, but not a selective COX-2 inhibitor nimesulide, attenuated the reductions of burrowing and open-field activity in response to a high dose of LPS injected intraperitoneally (Teeling et al., 2010). Since in both studies administration of COX inhibitors were able to down-regulate LPS-mediated sickness behaviors without causing significant differences in plasma and brain cytokine responses, they highlight the pivotal roles of COX in controlling sickness. Nevertheless, we cannot conclude that cytokines are not important mediators of sickness. Both IL-1β and TNF-α are known to up-regulate COX-2 in the brain (Lacroix and Rivest, 1998; Minghetti et al., 1999). Moreover, induction of cytokines and COX-dependent products could act together at the brain to achieve a full spectrum of sickness responses (Blatteis et al., 2005; Pecchi et al., 2006).

The last intriguing observation is that blocking increase of plasma cytokines or their systemic actions is not necessarily sufficient to suppress all symptoms of sickness. For instance, pretreatment with dexamethasone-21-phosphate or dexamethasone prevented peripheral LPS-induced hypothermia and the elevations of circulating cytokines, but it could not inhibit the decrements in burrowing, rearing, and open field activity (Murray et al., 2011; Teeling et al., 2010). Similarly, systemic injection of neutralizing antibodies against IL-1β, IL-6, or TNF-α before LPS treatment did not reverse the drop in burrowing or attenuate any increase of brain cytokine mRNA (Teeling et al., 2007), although in another study a pretreatment with anti-IL-6 but not anti-IL-1β antisera suppressed LPS-induced fever, anorexia, and the reduction in voluntary wheel running (Harden et al., 2006). Hence, solely managing plasma cytokines would not be a good therapeutic strategy to reduce sickness, especially if only one cytokine is reduced because different cytokines share many similar effects.

Therefore, these studies are not only supportive for cytokine-induced sickness, but they also highlight several key aspects of this model that are often neglected. Firstly, while most studies have measured cytokines in blood and at the brain, it is worth mentioning that cytokines arising at the inflammatory site could already signal to the brain via the fast neural routes and possibly be sufficient to initiate sickness (Campisi et al., 2003). This former event precedes the increases of plasma and brain cytokines, and probably also sensitizes the brain to the effects of cytokines (Dantzer, 2001, 2009). Secondly, although cytokines do regulate sickness, they are not the only factors governing sickness development. Other factors such as PGE_2 could alone or synergistically act with cytokines to elicit a full-blown sickness (Lazarus, 2006; Teeling et al., 2010, 2007). Thirdly, drugs that primarily target at the plasma cytokine profile are not ideal to control all symptoms of sickness (Murray et al., 2011; Teeling et al., 2010). Together with earlier studies showing that subdiaphragmatic vagotomy abrogated fever due to low doses of systemic LPS (Romanovsky et al., 1997) or IL-1β (Hansen et al., 2001) but not at high doses, and it was sufficient to attenuate behavioral depression even upon high doses of systemic LPS (Konsman et al., 2000) or IL-1β (Konsman et al., 2000; Wieczorek et al., 2005), it would be reasonable to speculate that circulating cytokines are more prominent in controlling thermoregulatory responses in sickness, whereas other sickness behavior changes depend more on neural pathways than on humoral cytokines.

The model of cytokine-induced sickness has been well established. Our next step should be to characterize how important cytokines are in mediating sickness under real life infections and injuries. Can pathological levels of cytokines alone be sufficient to initiate some, if not all, symptoms of sickness? To date, numerous animal experiments have studied the behavior and biochemical effects of either exogenous cytokines being injected individually at a dosage that cannot be reached by the body, or high amounts of purified PAMPs, e.g. LPS, which elicit many non-cytokine effects in animals. Their findings are certainly essential to our current understanding of cytokine-induced sickness, but they are not necessarily translatable to real life situations. Given that in vivo cytokines exert their effects at picomolar to nanomolar concentrations, and that multiple cytokines are simultaneously up-regulated and functionally interact to form cytokine networks, we suggest that our research should not just focus on the effects of mega doses of one single cytokine at a time, but instead should move to administering lower and physiologically reachable doses of multiple cytokines to investigate their combined effects. Hopefully, this will shed light on unraveling the importance of cytokines in delirium.

7. Conclusion

Cytokine-induced sickness is not new. For over two decades, we have built substantial knowledge in how systemic inflammation up-regulates cytokine levels, the effects of cytokines on behavior and fever, and the mechanisms by which systemic cytokines act at the brain. What we still need to clarify is the relative importance of cytokines, as compared to other mediators, in sickness during real life infections and injuries. Moreover, delirium can be

regarded as an extremity of sickness. While systemic inflammation causes sickness in young and non-dementia individuals, it precipitates delirium in aged and dementia patients. Whether elevated cytokines during systemic inflammation contribute significantly to delirium is still unclear, and this should also be our focus in the future.

Acknowledgement

The work on systemic cytokines and the brain in this laboratory is supported by Research Fund for the Control of Infectious Diseases (RFCID) of Food and Health Bureau, Hong Kong SAR government (09080822), and University (HKU) Alzheimer's Disease Research Network under Strategic Research Theme on Healthy Aging.

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