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Gateway reflex: Local neuroimmune interactions that regulate blood vessels

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ABSTRACT

Neuroimmunology is a research field that intersects neuroscience and immunology, with the larger aim of gaining significant insights into the pathophysiology of chronic inflammatory diseases such as multiple sclerosis. Conventional studies in this field have so far mainly dealt with immune responses in the nervous system (i.e. neuroinflammation) or systemic immune regulation by the release of glucocorticoids. On the other hand, recently accumulating evidence has indicated bidirectional interactions between specific neural activations and local immune responses. Here we discuss one such local neuroimmune interaction, the gateway reflex. The gateway reflex represents a mechanism that translates specific neural stimulations into local inflammatory outcomes by changing the state of specific blood vessels to allow immune cells to extravasate, thus forming the gateway. Several types of gateway reflex have been identified, and each regulates distinct blood vessels to create gateways for immune cells that induce local inflammation. The gateway reflex represents a novel therapeutic strategy for neuroinflammation and is potentially applicable to other inflammatory diseases in peripheral organs.

1. Introduction

The central nervous system (CNS) was long considered an immunologically privileged site. It has been characterized by a limited expression of MHC molecules within the parenchyma, a lack of endogenous professional antigen-presenting cells including dendritic cells, and the presence of a specialized structure of blood vessels called the blood-brain barrier (BBB) (Ransohoff et al., 2003). However, recent findings of the lymphatic system in the meninges (Louveau et al., 2015, 2017) challenge the dogma of the immune privilege of the CNS, instead suggesting some extent of inflow and outflow of immune cells into this vital organ. The gateway reflex is another mechanism that explains how immune cells enter the CNS. It assumes a “gateway” is generated at specific blood vessels. The presence of meningeal lymphatics and gateways in the CNS suggest physiological roles for immune cells in the CNS including immune surveillance. In addition, it is reported that the presence of lymphocytes including T cells in the CNS plays a role on cognitive functions and social behaviour in mice (Clark et al., 2018; Derecki et al., 2010; Kipnis et al., 2004; Wolf et al., 2009). Understanding how immune cells access the CNS could be used to prevent unwanted immune insults to this organ.

Multiple scolerosis (MS) is an autoimmune demyelinating disease of the CNS (Sospedra and Martin, 2005; Steinman, 2014). MS symptoms vary in patients and include visual disturbance, muscle weakness, difficulties in coordination and balance, congnitive problems, and bowel and bladder dysfunctions (Noseworthy et al., 2000). MS can be divided into several clinical types: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS) (Steinman, 2009, 2014). The most frequent form is RRMS, and a transition from RRMS to a progressive form is sometimes observed. However, what triggers this transition is not well understood. Genome-wide association studies (GWAS) have revealed that many genes involved in $CD4^+$ T cell activation, differentiation and survival are associated with MS (Consortium, 2011; Gregory et al., 2007). Indeed, the perivascular invasion of immune cells including $CD4^+$ T cells, $CD8^+$ T cells and macrophages is often observed in the demyelinated areas (Babbe et al., 2000). Immune cells further invade the brain parenchyma to trigger an autoimmune response against myelin antigens and cause CNS tissue damage. Data from MS animal models and GWAS revealed that autoreactive $CD4^+$ T cells play the central role in MS pathology, which is why these cells are key targets of MS research (International Multiple Sclerosis Genetics et al., 2007; Rangachari and Kuchroo, 2013). The inhibition of autoreactive $CD4^+$ T cell entry to the CNS is expected to block subsequent neuroinflammation in the CNS, thus making it a potentially effective treatment. Indeed, drugs that target $CD4^+$ T cell migration, including

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fingolimod and natalizumab, have shown clinical success (Pelletier and Hafler, 2012; Steinman, 2005). Further insights into the T cell invasion process to the CNS should help identify novel therapeutic targets for CNS inflammatory diseases including MS.

2. Gravity regulates the entry point of autoreactive CD4$^+$ T cells into the CNS

It is known that gravity stimulation is required to maintain physical functions such as muscle strength and bone mass (Petersen et al., 2017; Sibonga, 2013). In addition, some astronauts after staying at the International Space Station claimed ophthalmic changes including optic disc edema, which is evidence of endothelial dysfunction and inflammatory symptoms (Mader et al., 2011; Zwart et al., 2017). However, neither the direct contribution of gravity stimulation to local inflammation nor its mechanism are fully understood. We serendipitously found that gravity stimulation establishes a gateway for autoreactive CD4$^+$ T cells in specific spinal cord vessels to invade the CNS (Arima et al., 2012). Using mouse models for chronic inflammatory diseases such as MS and rheumatoid arthritis (RA), we previously found that type I collagen-positive non-immune cells such as endothelial cells and fibroblasts play an important role in the induction of inflammatory responses through their soluble factor-mediated interactions with immune cells (Ogura et al., 2008; Sawa et al., 2006). Upon the ligand-induced simultaneous activation of NF-κB and STAT3 by IL-17 and IL-6 for instance, non-immune cells produce large amounts of pro-inflammatory mediators, such as various chemokines, cytokines and growth factors. This concomitant activation of NF-κB and STAT3 significantly enhances NF-κB activity to promote the transcription of NF-κB target genes (Atsumi et al., 2017; Harada et al., 2015; Meng et al., 2016; Murakami et al., 2011, 2013; Ogura et al., 2008; Sawa et al., 2006). This promotion was shown to be a key element for the induction of experimental autoimmune encephalomyelitis (EAE), an animal model of MS (Arima et al., 2012; Murakami et al., 2013; Ogura et al., 2008), cytokine-induced RA model (Atsumi et al., 2017; Harada et al., 2015; Meng et al., 2016; Murakami et al., 2011, 2013) and allogeneic transplantation (Lee et al., 2012). We termed the inflammation-inducing mechanism based on the synergistic effect of NF-κB and STAT3 in non-immune cells as the inflammation amplifier (Atsumi et al., 2014; Nakagawa et al., 2015) (Fig. 1). Interestingly, patients with chronic inflammatory diseases including MS show higher levels of target molecules of the inflammation amplifier in their serum than do healthy volunteers, and activation of NF-κB and STAT3 can be observed in tissue sections from those patients (Harada et al., 2015; Lee et al., 2013; Murakami et al., 2013), suggesting that the inflammation amplifier is activated in humans as well.

During the course of these studies on chronic inflammation, we investigated where myelin-autoreactive CD4$^+$ T cells in the circulation initially attack the CNS during EAE, because EAE typically develops from the tail tip of mice despite the wide distribution of myelin in the CNS, suggesting the existence of a unique entry point. To track autoreactive CD4$^+$ T cells, we employed an adoptive transfer model of EAE, in which neuroinflammation is induced in naïve mice by a single intravenous injection of pathogenic CD4$^+$ T cells against myelin oligodendrocyte glycoprotein (MOG) (Tanaka et al., 2017a). This model can exclude any potential effects of Freund's complete adjuvant and pertussis toxin, which are usually used in the active immunization model of EAE, on the migration of pathogenic CD4$^+$ T cells. The transfer EAE model induces a clear and transient clinical symptom, typically starting from a loss of tonicity at the tail tip. At a preclinical stage of transfer EAE, immunohistochemistry of whole-mount sections of adult recipient mice using the Kawamoto method (Kawamoto, 2003) and subsequent flow cytometry analysis successfully revealed that transferred pathogenic CD4$^+$ T cells mainly accumulated at the dorsal vessels of the fifth lumbar (L5) spinal cord, but not in the brain or other spinal cord vessels (Arima et al., 2012). Consistently, many chemokines including CCL20, a chemokine that recruits pathogenic CD4$^+$ T cells, were increased at the L5 dorsal vessels compared with the dorsal vessels of the other spinal cord levels (Arima et al., 2012). This selective accumulation of pathogenic CD4$^+$ T cells at the L5 dorsal vessels was abrogated by the conditional knockout of STAT3 in type I collagen-positive non-immune cells, indicating dependency on the inflammation amplifier (Atsumi et al., 2014; Nakagawa et al., 2015). These results suggest that the L5 dorsal vessels are one gateway to the CNS for pathogenic CD4$^+$ T cells in the transfer EAE model (Fig. 2).

What is the mechanism underlying the selective upregulation of chemokines at the L5 dorsal vessels? An interesting answer was derived from casual discussions with a researcher in the field of space physiology. It is known that the dorsal root ganglion (DRG) of the L5 segmental level contains sensory afferent neurons that are reactive to

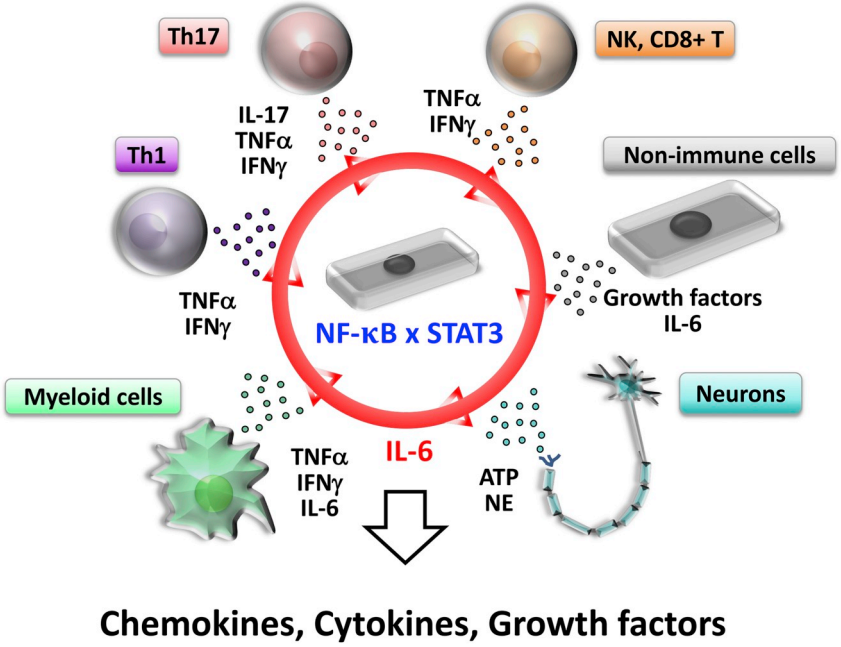

Fig. 1. Inflammation amplifier.
The inflammation amplifier is an inflammatory mechanism in which simultaneous activation of two transcription factors, NF-κB and STAT3, in non-immune cells including endothelial cells and fibroblasts induces a massive production of inflammation factors such as chemokines, growth factors and IL-6. Various factors activating NF-κB and STAT3 such as IL-17, TNFα and IL-6 are found to activate the inflammation amplifier. Neurotransmitters such as ATP and norepinephrine (NE) are found to enhance NF-κB activation, which sustains the inflammation amplifier. IL-6 is both induced by the inflammation amplifier and stimulates the inflammation amplifier, thus creating a positive feedback loop. The local production of chemokines, growth factors and IL-6 by the inflammation amplifier play an essential role in the pathogenesis of many chronic inflammatory diseases. IFN, interferon; NE, norepinephrine; NK, natural killer cells; Th, helper T cells; and TNF, tumor necrosis factor.

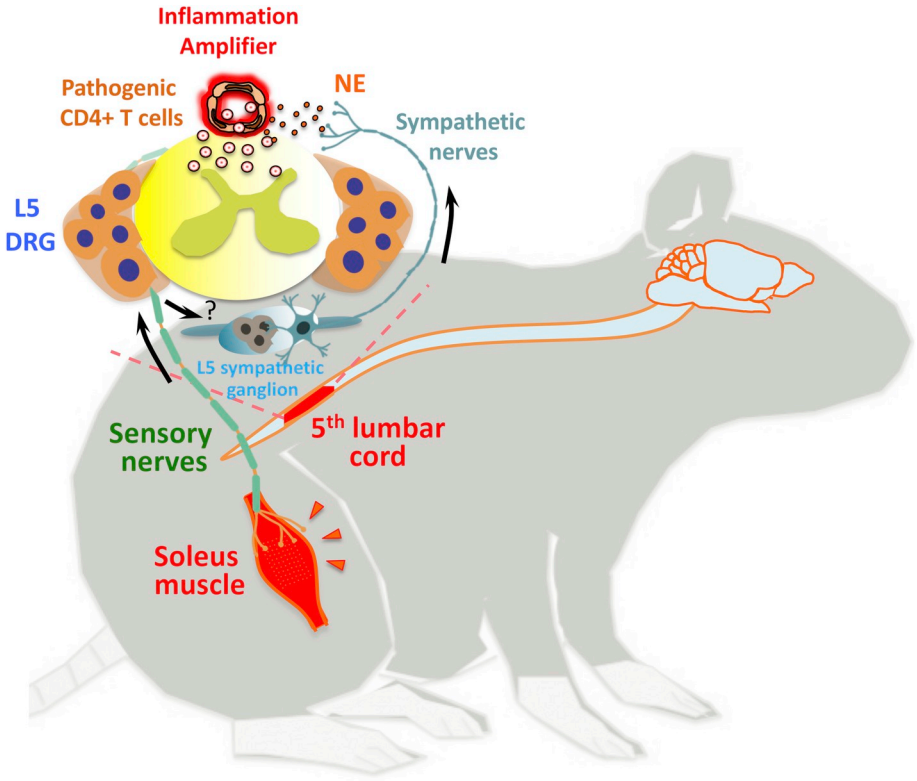

Fig. 2. Gravity gateway reflex.
Gravity stimulation activates sensory nerves in the soleus muscles, whose cell bodies are located at the dorsal root ganglion (DRG) of the fifth lumbar (L5) spinal cord. Neural signals to L5 DRG neurons are transmitted to the L5 sympathetic ganglion via an unidentified pathway, followed by norepinephrine (NE) secretion at the L5 dorsal vessels. NE enhances the inflammation amplifier at the L5 dorsal vessels to induce chemokine expression, causing the invasion of pathogenic $CD4^+$ T cells from the vessels.

gravity stimulation. Altered gravity burden created by the parabolic flight of a jet airplane showed that the afferent input of the L5 neurons is closely associated with the activity of the soleus muscles (Kawano et al., 2002). In fact, the L5 DRG is large in both mice and human, partly because the L5 DRG neurons are constantly activated by gravity (Ohira et al., 2004; Shen et al., 2006). These facts led us to examine the possibility that gravity influences inflammation by using a tail-suspension assay that unloads the hindlegs of mice from gravity burden (Morey-Holton and Globus, 2002). As hypothesized, the tail suspension significantly decreased chemokine expression in the L5 vessels, but upregulated it in the dorsal vessels of the cervical spinal cord due to the increased body weight load on the forelegs. In addition, when the soleus muscles were electrically stimulated during the tail suspension, chemokine expression in the L5 vessels was recovered (Arima et al., 2012). Consistently, tail suspension improved the clinical scores of transfer EAE (Arima et al., 2012). These results indicate that the activity of the soleus muscles affects the behaviour of pathonic $CD4^+$ T cells (Arima et al., 2012). Furthermore, we found that neurons in the sympathetic ganglions were more activated at the L5 level than the L1 level and that the pharmacological blockade of adrenergic receptors inhibited chemokine expression at the L5 dorsal vessels and lowered EAE clinical stores (Arima et al., 2012). Although experimental evidence for neural connections between neurons in the L5 DRG and L5 sympathetic ganglions remains to be proven, these experimental data strongly suggest functional interactions between them. Thus, the results revealed a novel local neuroimmune interaction, where regional neural activation controls specific blood vessels to upregulate chemokines, creating a gateway for immune cells to enter the CNS (Fig. 2), i.e. the gateway reflex (Andersson and Tracey, 2012a; Chavan et al., 2017; Deutschman and Tracey, 2014; Ohki et al., 2017; Pavlov and Tracey, 2017; Sabharwal et al., 2014; Tanaka et al., 2017b; Tracey, 2012, 2016).

3. Pain sensation boosts neuroinflammation

Other neural stimulations were tested to extend the concept of the gateway reflex. Pain is a tonic sensory stimulus and an undesiable symptom that significantly compromises the quality of life in patients with various diseases and injuries (Bennett and Woods, 2014; Feinstein et al., 2014; Morales-Lazaro et al., 2013). A positive correlation between disease symptoms and the degree of pain is reported in MS patients (Ehde et al., 2003; Ehde et al., 2006; O'Connor et al., 2008), and hyperalgesia is reported in EAE models (Khan and Smith, 2014; Lu et al., 2012). However, another report found no relation between pain and disease course in MS (Kalia and O'Connor, 2005). This inconsistency could be in part because the evaluation of pain sensation is largely dependent on self-reporting. Thus, besides serving as an alarm about some abnormality in the body, the role of pain in disease and injury is not clear.

The trigeminal nerves are composed of three main branches, and the middle branch mainly contains sensory nerves. To induce pain sensation, we performed a partial ligation of the middle branch of the trigeminal nerves in the transfer EAE model. Pain induction on the day of the adoptive transfer of pathogenic $CD4^+$ T cells significantly prolonged the disease symptom (Arima et al., 2015). The transfer EAE model we used induces a transient disease and does not show relapses under a normal rearing condition (Arima et al., 2015; Tanaka et al., 2017a). Interestingly, the induction of pain during the remission phase resulted in a clear relapse of EAE. In addition to the nerve ligation, the injection of capsaicin, which produces pain sensation through nociceptors including TRPV1 (Davis et al., 2000), at the cheek or forepaw of mice recovered from transfer EAE (hereinafter referred to as EAE-recovered mice) also caused relapse (Arima et al., 2015). Furthermore, pain medicines such as gabapentin or pregabalin suppressed the pain-induced relapse in the transfer EAE model and spontaneous relapse in another relapsing-remittent EAE model in SJL mice (Arima et al., 2015). These results uncovered an additional role of pain sensation in promoting neuroinflammation in the CNS.

Usually, EAE-recovered mice do not show clinical signs of EAE in appearance, however, immunohistochemistry revealed that activated monocytes expressing high levels of MHC class II abundantly resided around the meninges of the L5 spinal cord, which is the first inflammation site of EAE (Arima et al., 2015). Parabiosis experiments

joining two mice with different congenic markers before EAE induction demonstrated that the MHC class II high monocytes found in the L5 cord during the remission phase were derived from the periphery (Arima et al., 2015). Interestingly, after pain induction, these cells accumulated at the bilateral ventral vessels of the L5 spinal cord. The L5 dorsal vessels are affected by the gravity gateway reflex, as explained above (Arima et al., 2012), whereas the pain-mediated neural activation controls ventral vessels (Arima et al., 2015), suggesting that different neural activations regulate unique sets of blood vessels. The depletion of MHC class II high monocytes by clodronate liposomes in the remission phase suppressed the invasion of pathogenic $CD4^+$ T cells and EAE relapse after pain induction, indicating a key pathogenic role of MHC class II high monocytes (Arima et al., 2015). These monocytes express CX3CR1 receptor, produce the chemokine CX3CL1 after stimulation with norepinephrine (NE), and have antigen-presenting ability to activate pathogenic $CD4^+$ T cells in vitro (Arima et al., 2015). In addition, an inhibitor of NE β1 receptor and chemical sympathectomy abrogated the pain-induced EAE relapse. These results suggest the following chronological scenario: (i) pain induces NE secretion around the ventral vessels of the L5 cord via sensory-sympathetic interactions, (ii) MHC class II high monocytes accumulate around the ventral vessels through the auto/paracrine action of the CX3CL1-CX3CR1 axis, (iii) circulating pathogenic $CD4^+$ T cells are activated by MHC class II high monocytes around the ventral vessels, and finally (iv) invasion of the pathogenic $CD4^+$ T cells and EAE relapse (Fig. 3). Pain induction in mice stimulates c-fos expression (i.e. neural activation) in the L1 as well as L5 sympathetic ganglia, suggesting multiple levels of the spinal cord are affected. Since the L5 spinal cord is the initial inflammation site in the gravity gateway reflex and contains MHC class II high monocytes more abundantly than other levels of the spinal cord during the remission phase of EAE, the relapse response is most evident in the L5 spinal cord (Arima et al., 2015). Because MHC class II high monocytes have a relapse-inducing capacity and persist in the CNS for a long period, targeting the presumptive survival factor(s) for these cells could be a novel therapeutic strategy for MS relapse. Further experiments using knockout mice and chemical activators and inhibitors revealed that a specific neural pathway involving TRPV1/Nav1.8-expressing sensory neurons, a pain processing region in the brain (the anterior cingulate cortex (ACC)), and sympathetic neurons that distribute to the ventral vessels of the spinal cord is responsible for the pain-induced relapse (Fig. 3) (Arima et al., 2015). Since neutralization of IL-17 and IL-6, typical cytokines that activate the inflammation amplifier (Atsumi et al., 2014; Nakagawa et al., 2015), suppressed the pain-induced relapse without affecting the accumulation of MHC class II high monocytes in the L5 ventral vessels, we concluded that the inflammation amplifier is involved in pain-induced EAE relapse downstream of the activation of MHC class II high monocyte-mediated pathogenic $CD4^+$ T cells around the L5 ventral vessels.

4. Activation of neural pathways by brain microinflammation induces dysfunction in peripheral organs

Chronic mental stresses are known to have a negative impact on chronic illnesses and sometimes cause gastrointestinal and cardiovascular dysfunctions (Esler, 2017; Konturek et al., 2011). Mental stresses are sensed as neural activations in specific brain regions involving the paraventricular nucleus of the hypothalamus (PVN), dorsomedial hypothalamic nucleus (DMH), dorsal motor nucleus of the vagus nerve (DMX), and the vagus nerve circuit (Ulrich-Lai and Herman, 2009). In addition, the association of MS with mental illnesses and gastrointestinal failures has been reported (Goldman Consensus, 2005; Gupta et al., 2005; Kimura et al., 2000; Marrie et al., 2015; Pokorny et al., 2007; Rang et al., 1982; Sadovnick et al., 1989). These facts led us to examine an involvement of the gateway reflex during chronic stress-mediated pathology.

We tested whether chronic stress can change the entry point of immune cells from the L5 gateway to elsewhere in transfer EAE mice. To do so, a sleep disorder model was used, in which chronic stress is induced in mice housed in a free rotation wheel while perpetually deprived of water (Miyazaki et al., 2013; Oishi et al., 2014). To our surprise, the sleep disorder in the transfer EAE model resulted in a high rate of mortality compared with mice who did not show the usual paralysis symptoms of EAE (Arima et al., 2017). On the other hand, sleep disorder or transfer EAE alone did not cause sudden death. Another chronic stress model using damp cage bedding also caused sudden death when combined with transfer EAE model, suggesting that chronic stress is a responsible factor. Under normal rearing, transfer EAE induces neuroinflammation from the dorsal vessels of the L5 spinal cord

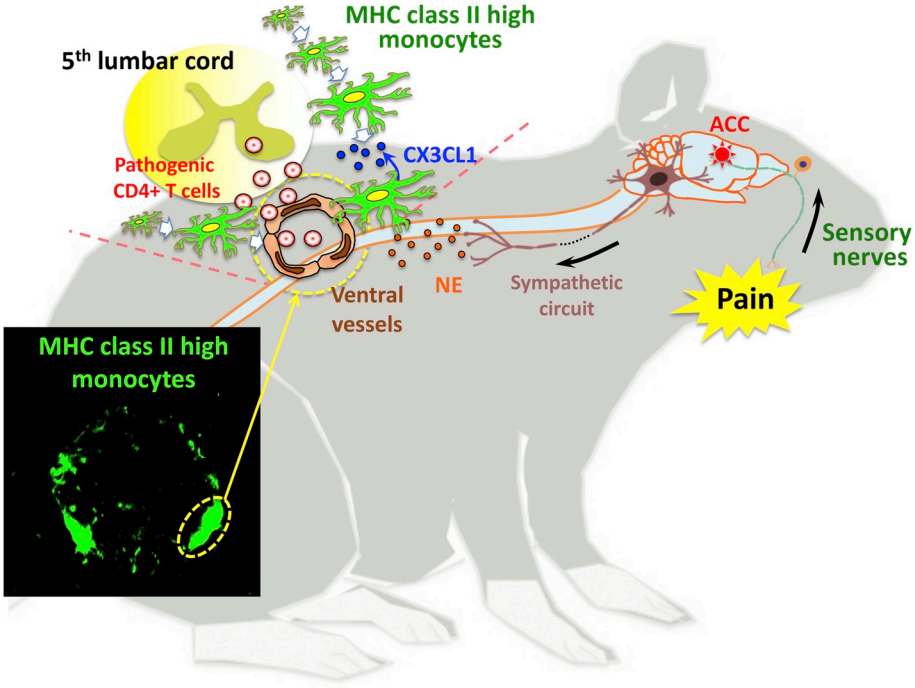

Fig. 3. Pain gateway reflex.
Pain induces sensory nerve stimulation, which sends signals to the anterior cingulate cortex (ACC), a pain-processing area in the brain. Following activation of specific sympathetic circuits, CX3CL1 expression is induced around the ventral vessels of the spinal cord in a norepinephrine (NE)-dependent manner. CX3CL1 recruits MHC class II high monocytes around the ventral vessels. Because the L5 spinal cord, which is the initial inflammatory lesion of transfer EAE, contains a large number of MHC class II high monocytes in EAE-recovered mice, the L5 region is affected most after pain induction. MHC class II high monocytes present MOG antigens to activate circulating pathogenic $CD4^+$ T cells in the L5 ventral vessels causing disease relapse. The photograph is a coronal section of the L5 spinal cord and shows an accumulation of MHC class II high monocytes by immunostaining with anti-MHC class II (green).

owing to the gravity gateway reflex, and the clinical symptom starts with a loss of tail tip tonicity (Arima et al., 2012). However, in the case of transfer EAE under chronic stress, immune cell invasion was not evident at the L5 spinal cord. Instead, pathogenic $CD4^+$ T cells and periphery-derived MHC class II high monocytes were found around bilateral blood vessels surrounded by the dentate gyrus (DG), thalamus and third ventricle (3V). Chemokine induction is a responsible phenomenon for gateway formation, and we found that neutralization of CCL5 abrogated the sudden death caused by transfer EAE under chronic stress. CCL5 expression in the specific bilateral vessels was induced by chronic stress alone, but not by the transfer EAE model (Arima et al., 2017), suggesting chronic stress-induced neural inputs induces CCL5 upregulation (i.e. gateway formation) in the specific vessels. Regional neural signaling between the PVN, which senses stress, and the specific blood vessels at the boundary of the DG, thalamus and 3V would be supported if both areas were connected by neurons. Indeed, neural tracing experiments identified a direct neural link via tyrosine hydroxylase-positive noradrenergic nerves. These results demonstrate that chronic stress can activate the stress gateway reflex to migrate immune cells from the L5 dorsal vessels to specific brain bilateral vessels by CCL5 upregulation through a neural circuit that connects with the PVN (Fig. 4) (Arima et al., 2017).

However, neuroinflammation at the specific bilateral vessels at the boundary of DG, thalamus and 3V cannot directly explain the high rate of mortality in EAE mice with chronic stress. We found that the DMH was highly activated in EAE mice with chronic stress, and identified a neural connection between it and the specific vessels (Arima et al., 2017). In other words, an otherwise resting neural pathway is hyperactivated in mice with chronic stress plus an infusion of pathogenic $CD4^+$ T cells. To activate neural pathways, a neurotransmitter is required. ATP is typically thought of as an essential energy source, but it also acts as a neurotransmitter and proinflammatory factor through receptors such as P2RX7 (Burnstock, 2006; Di Virgilio et al., 2017). The injection of ATP to specific blood vessels at the boundary area of the DG, thalamus and 3V induced sudden death in chronically stressed mice without transfer EAE. By contrast, intracranial injection of a P2RX7 antagonist to the specific vessels prevented the mortality. c-Fos induction (i.e. neural activation) in the DMH region was also significantly inhibited by P2RX7 antagonism at the specific vessels in EAE mice with chronic stress. These results suggest ATP at the microinflammation sites around the specific vessels is a neurotransmitter that activates a new neural pathway toward DMH (Arima et al., 2017), suggesting that the immune response stimulates the neural activation. The DMH, which is hyper-activated in stressed EAE mice, is known to connect to the DMX. The vagus nerve pathway is known to cause epithelial damages in the stomach via an overproduction of gastric acid when hyper-activated (Okumura et al., 1990; Schubert, 2003). Additionally, in stressed EAE mice, epithelial damage in the upper gastrointestine and bloody feces were evident (Arima et al., 2017). As expected, surgical vagotomy prevented the sudden death of EAE mice under chronic stress condition (Arima et al., 2017). Therefore, the stress gateway reflex excessively enhances a stress response through a collateral event of neuroinflammation at vessels that activate a neural pathway involving the DMH, DMX and vagus nerves. The stress gateway reflex also revealed a bidirectional communication between the immune system and nervous system. Namely, neural activations in the PVN affect chemokine expressions at the specific brain vessels, and ATP release owing to microinflammation at the specific brain vessels influences neural activations involving the DMH, DMX and vagus nerves. Excessive activation of the vagus nerves in stressed EAE mice caused sudden death by heart failure, in part due to an increase in plasma potassium levels caused by gastrointestinal bleeding (Arima et al., 2017) (Fig. 4). Changing the EAE pathology from the usual symptom (i.e. ascending paralysis from the tail tip) to a severe and fatal disease may represent a mechanism that explains the transition of MS to progressive forms.

We sought to generalize this phenomenon beyond transfer EAE. Besides the adoptive transfer of pathogenic $CD4^+$ T cells, neuroinflammation caused by a direct injection of cytokines or activated immune cells around the specific vessels in the brain also caused sudden death in mice under chronic stress (Arima et al., 2017). Thus, microinflammation in specific brain vessels adjacent to the DG, thalamus and 3V drives the stress gateway and mediates the fatal pathology in the periphery (Fig. 4). Brain micro-inflammation is observed in Alzheimer's disease, non-Alzheimer-type dementia, Parkinson's disease, psychological disorders and epilepsy (Appel et al., 2010; Najjar et al., 2013; Togo et al., 2002; Vezzani et al., 2011). Further, it potentially activates new neural pathways to disturb neural networks and contributes to the pathology and comorbidity of these diseases. The stress gateway reflex

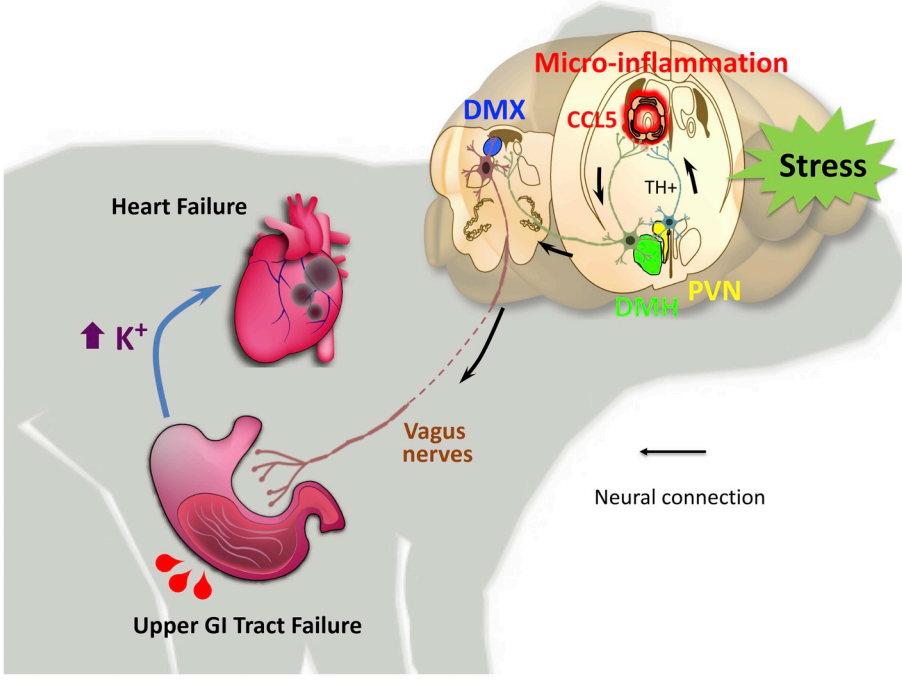

Fig. 4. Stress gateway reflex.
Under a chronic stress condition, EAE mice show a high rate of sudden death with severe gastrointestinal and heart failure. Chronic stress induces activation of the paraventricular nucleus in the hypothalamus (PVN), which then stimulates tyrosine hydroxylase + neurons that are connected to specific vessels surrounded by the ventricle dentate gyrus, thalamus, and third and upregulate CCL5. Micro-inflammation at the specific brain vessels triggered by CCL5-mediated pathogenic $CD4^+$ T cell invasion activates a neural pathway at the dorsomedial nucleus of hypothalamus (DMH) through the production of ATP. Thus, the communication between the immune and nervous systems by stress gateway reflex is bidirectional. Hyperactivation of the DMH transmits signals to efferent vagus nerves via the dorsal motor nucleus of the vagus nerve (DMX), causing severe upper gastrointestine (GI) tract failure. An elevation of potassium ion levels in the blood caused by severe GI bleeding eventually induces heart failure, which is associated with cardiac myocyte death.

also has an implication in the brain-gut axis. Recent studies suggest that gut microbiota are altered in neurological and psychiatric disorders, and chronic stress can change the gut microbiome in mice (Fung et al., 2017; Gao et al., 2018). The gut is rich in nerves that form the enteric nervous system, which is sometimes called the second brain (Chalazonitis and Rao, 2018). In addition, there are intriguing reports that show direct or indirect interactions of gut bacteria with vagal afferents (Cawthon and de La Serre, 2018) and direct stimulation of sensory neurons by certain bacteria (Chiu et al., 2013). Thus, it is tempting to speculate whether gut microbiota-mediated stimulations of the enteric nervous system and/or vagal afferents modulate certain unique blood vessels in the brain to trigger the gateway reflex.

5. Future perspectives

Here we summarized a recently emerged local neuroimmune interaction, the gateway reflex. Another local neuroimmune interaction, called the inflammatory reflex or cholinergic anti-inflammatory pathway, induces a suppressive effect on inflammation and has already been tested in a clinical setting with promising results (Andersson and Tracey, 2012a; b; Chavan et al., 2017; Koopman et al., 2016; Pavlov and Tracey, 2017; Tracey, 2016). The concept of the gateway reflex can also be applied to clinical purposes if the precise neural networks are delineated and an appropriate stimulation is developed. Encouragingly, weak electric stimulation in different muscles of mice induces chemokine upregulation, namely gateway formation, at different blood vessels of the spinal cord depending on the stimulated muscles (Fig. 5) (Arima et al., 2012). This finding suggests it is possible to artificially control the gateway reflex. As for delineation of the neural pathways, recent advances in analytic technologies including tissue clearing reagents such as CUBIC, CALRITY, Scale and PACT (Chung et al., 2013; Hama et al., 2011; Susaki et al., 2014; Tainaka et al., 2014, 2016; Yang et al., 2014); transgenic mice reporting neural activations such as GCaMP, Arc-dVenus and cFos-GFP mice (Barth et al., 2004; Chen et al., 2012; Eguchi and Yamaguchi, 2009); artificial control of neural activation and suppression by optogenetics and chemogenetics (Campbell and Marchant, 2018; Kim et al., 2017); various viral and chemical neurotracers (Zeng, 2018); and neuron mapping with a RNA barcoding system (Kebschull et al., 2016) will be useful. Because neural pathways are distributed throughout the body, it is expected that identifying additional gateway reflexes and novel local neuroimmune interactions will contribute to therapeutic strategies for various neuroimmune and chronic inflammatory diseases.

Conflicts of interests statement

We have no potential conflict of interests regarding this article.

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Abbreviations

ACC	anterior cingulate cortex
ATP	adenosine triphosphate
BBB	blood-brain barrier
CNS	central nervous system
DG	dentate gyrus
DMH	dorsomedial hypothalamic nucleus
DMX	dorsal motor nucleus of the vagus nerve
DRG	dorsal root ganglion
EAE	experimental autoimmune encephalomyelitis
GI	gastrointestine
L	lumbar
MS	multiple sclerosis
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
PVN	paraventricular nucleus of the hypothalamus
RA	rheumatoid arthritis
STAT	signal transducer and activator of transcription
TRPV1	transient receptor potential vanilloid 1

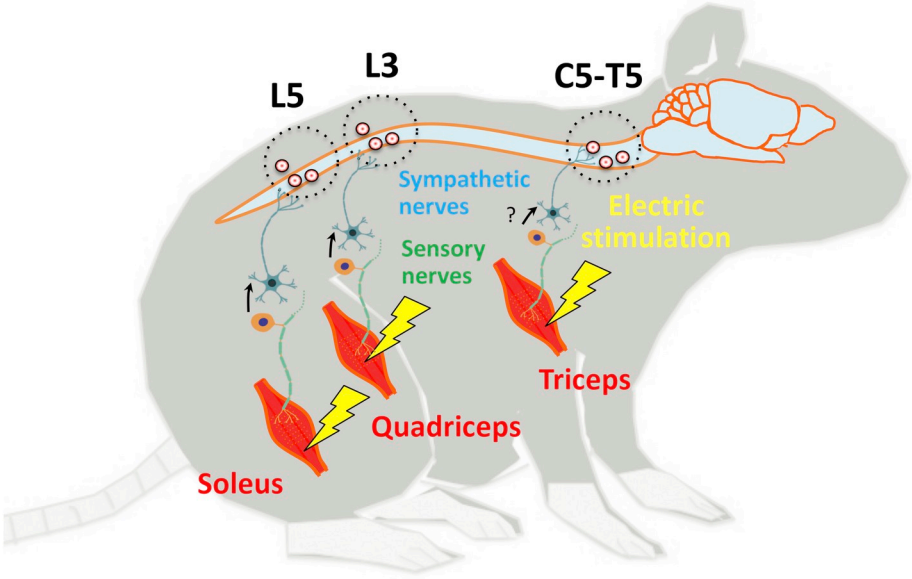

Fig. 5. Electric gateway reflex.
Weak electric stimulation to the muscles can control the gateway reflex via the activation of specific sensory and sympathetic nerves. Electric pulses to the triceps induces chemokine expression at the dorsal vessels of the lower cervical (C) to upper thoracic (T) spinal cord. Likewise, electric stimulation of the quadriceps or soleus muscles induces a gateway at the L3 or L5 dorsal vessels, respectively. This electic gateway reflex can potentially be used for clinical application.

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