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Chapter 7

In Vivo Imaging of Septic Encephalopathy

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Abstract

Septic encephalopathy is a devastating symptom of severe sepsis. Many studies have been performed to uncover the pathophysiological mechanisms of septic encephalopathy; however, novel technical approaches are still required to overcome this complex symptom. Because patients are suffering from severe cognitive impairment, coma, or delirium, which burden not only patients but also caregivers, overcoming septic encephalopathy is still a major social problem worldwide, especially in the intensive care. Septic encephalopathy seems to be caused by cytokine invasion and/or oxidative stress into the brain, and this pathological state leads to imbalance of neurotransmitters. In addition to this pathophysiology, septic encephalopathy causes complicated symptoms (e.g., ischemic stroke, edema, and aberrant sensory function). For these pathophysiological mechanisms, electrophysiology using animal models, positron emission tomography (PET), computed tomography, and magnetic resonance imaging for septic patients has provided important clues. However, the research for septic encephalopathy is currently confronted with the difficulty of complex symptoms. To overcome this situation, in this chapter, we introduce our novel methods for in vivo imaging of septic encephalopathy using near infrared (NIR) nanoparticles, quantum dots. In addition to our recent progress, we propose a strategy for the future approach to in vivo imaging of septic encephalopathy.

Keywords: septic encephalopathy, molecular mechanism, in vivo imaging, quantum dots, disseminated intravascular coagulation

1. Introduction

Although the pathophysiological mechanism of septic encephalopathy (SE) still includes some mystery, recent progress of challenging research using animal models of sepsis has

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gradually uncovered the molecular pathogenesis of SE. For instance, recent pathophysiological findings for SE include synaptic deficiency by interleukin-1 beta [1] and acetylcholine [2] and brain ischemia or edema with disseminated intravascular coagulation (DIC) [3]. These phenomena are dynamically altered in a time-dependent manner based on the content of symptoms. Functional magnetic resonance imaging (fMRI) for patients of SE can describe the status of symptoms; however, it is difficult to track these time-dependent changes in the septic brain because of the low time resolution of its measurement. To overcome this technical difficulty, we are working to develop noninvasive near infrared (NIR) imaging as a novel method to analyze the pathological state of SE.

In this chapter, we introduce current understanding of pathophysiology, the imaging technology, and the application of novel imaging technology to visualize the pathophysiological mechanism of SE. The contents are described as follows: (1) etiology of SE, (2) molecular mechanisms of pathogenesis, (3) NIR in vivo imaging, and (4) application to SE. In particular, we focus on DIC and our approach firstly demonstrates the novel application of NIR in vivo imaging to DIC. We expect that this review will be helpful to readers such as basic biomedical students, and scientists who are interested in the future preclinical and clinical application to SE.

2. Septic encephalopathy (SE)

Septic encephalopathy (SE) is a symptom with brain dysfunction caused by sepsis. Up to 70% of severe septic patients encountered developed SE [4]. Patients with SE are often suffering from various neurological symptoms. Many research reports and reviews have discussed cognitive impairment [5, 6], delirium [7], coma [8–11], and recently seizure and aberrant sensory function [12–16]. In addition, complication symptoms such as ischemic stroke, edema, etc. occurred [17–19]. However, not all of pathophysiological mechanisms for SE have been clarified in Ref. [20], and a better understanding of SE is still an important social problem worldwide [21].

2.1. Etiology

The SE is often found in acute liver failure and cirrhosis patients and triggered by the various chemical mediators followed by systemic inflammatory response syndromes, whole-body inflammation [22–24]. SE is different from the brain "encephalitis" which occurs due to pathogens (e.g., bacteria, virus, etc.) direct invasion into the brain. Rather than the direct invasion, SE is caused indirectly by excessive inflammatory response (e.g., cytokine storm). Thus, SE is a symptom. Clinical studies for SE reported that patients with SE often suffered from hypotension [25], imbalance of amino acids in plasma [26], and neuronal injury with edema [27, 28]. Several lines of evidences suggest that a rodent model of SE showed aberrant behavior: altered sensory function [29, 30], increased anxiety [31, 32], and cognitive impairment [33]. These results are similar to the symptoms of brain dysfunction in SE patients [34]. Thus, neurological impairment leads to various symptoms in SE.

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3. Molecular mechanisms

3.1. Pathogenesis

To understand the molecular mechanisms, pathophysiological factors (e.g., imbalance of chemical substances, cellular environment, and molecules) are discussed. Overall pathogenesis for SE is summarized in **Figure 1**. When SE is occurred, various chemical substances (e.g., neurotransmitter, modulator, etc.) were involved as reviewed elsewhere in Refs. [35, 36]. These chemical substances were mainly important for maintaining homeostasis in the normal condition. After the SE occurred, the imbalanced rate of substances (e.g., amino acids) [37–41] abrogated brain metabolic function (e.g., tryptophan metabolism) [42–44], microglial activation in the brain followed by detachment of pericyte from microvascular basal lamina [45, 46].

Normally, the brain is protected with a barrier called blood brain barrier (BBB). The barrier consists of brain endothelial cells, and these cells are tightly attached with tight junction. The barrier is selectively permeable to transport of amino acid, gas, and lipid-soluble chemicals which are important for neuronal function. Therefore, the inflammatory molecules cannot affect brain function in the normal condition because the brain is protected with blood brain barrier, and foreign substances are impeded by this barrier.

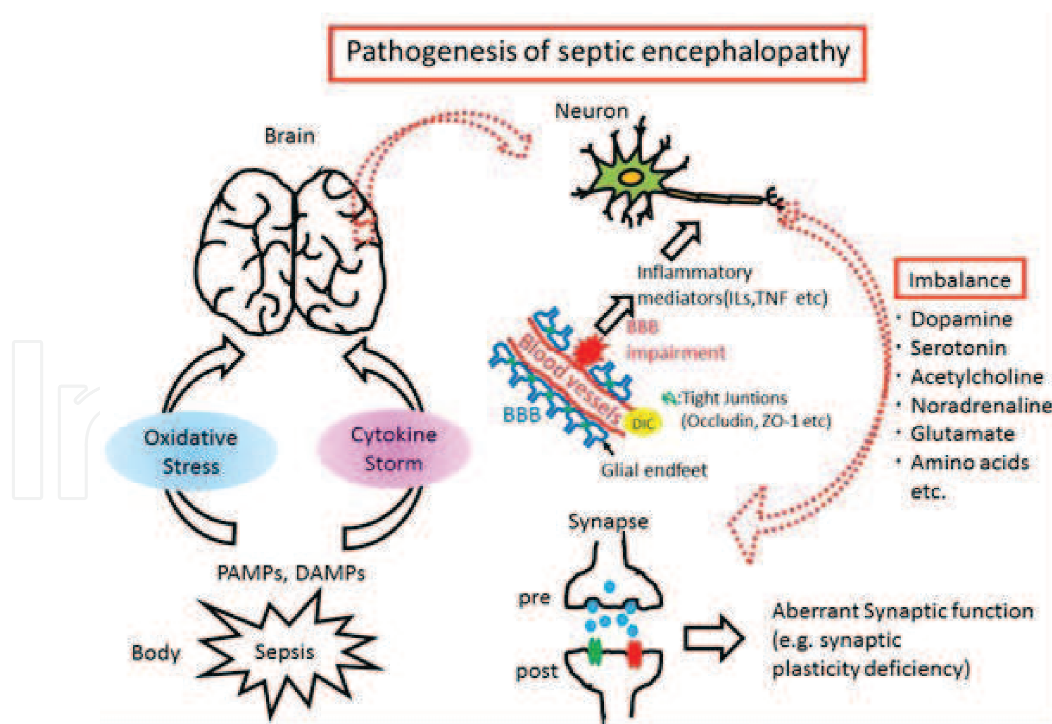

Figure 1. Overview of pathogenesis for septic encephalopathy (SE). Severe sepsis often results in septic encephalopathy, mainly followed by oxidative stress and cytokine storm. Accompanying BBB impairment and DIC, invaded inflammatory mediators cause aberrant neuronal function. PAMPs: pathogen-associated molecular pattern; DAMPs: damage-associated molecular patterns; BBB: blood brain barrier; IL: interleukin; TNF: tumor necrosis factor.

In the septic condition, occurrence of systemic inflammatory response syndromes is followed by sepsis, the syndromes lead to destruction of this blood brain barrier [47, 48], and harmful chemical substances disrupt normal brain function. Then, the chemical substances cause the aberrant neuronal transmission and plasticity [1, 30]. The components of tight junctions are claudin, occludin, zona occludin, etc. [49]. This tight junction serves as if an adhesive of cells and underpins the blood brain barriers. Using a mouse model of sepsis, we clearly demonstrated that the occludin protein was destroyed 20 h after induction of sepsis and led to a permeabilization of cytokine [1, 30]. Other groups reported that tumor necrosis factor (TNF)-alpha and calcium-binding proteins were increased in the SE [50].

3.2. Blood brain barrier (BBB) impairment

Why was the tight junction disrupted? Overall mechanisms are still unclear, a hypothesis is, however, addressed. Neuroinflammation (e.g., microglia/macrophage activation, nitrogen oxide gas production) resulted in the mitochondria dysfunction with reactive oxygen synthesis (ROS) [51–55] and dysfunction of cerebrovascular endothelial cells [56]. The process is impeded by ROS inhibitors [57] or mitochondria-targeted peptides [55].

Another hypothesis is as follows. Septic patients sometimes showed a rapid vasoconstriction of blood vessels, and this mechanical alteration may cause the damage to the microvasculature structure [58, 59]. Endothelin and its receptor which constrict blood vessels might be involved in that process [60, 61]. Phosphoinositide 3-kinase cascade activated microglial cell and matrix metalloproteinase (i.e., marker of inflammation) and aggravated BBB impairment [62]. Consequently, the BBB disruption finally leads to the invasion of inflammatory mediators into the brain of SE [63].

3.3. Effect of cytokine storm on brain function

In any case, the dysfunction of blood brain barrier after sepsis increases the permeability of inflammatory molecules as described below and finally causes the brain malfunction.

For example, there are widely discussed cytokines such as interleukins (interleukin-1, -6, -10) [37, 64], tumor necrosis factor (TNF)-alpha [65, 66], complement C5a [67], and cascade [68]. Epigenetic modulation (e.g., histone acetylation) participates in the trigger of aberrant glutamate receptor subunits [29, 69] and causes memory deficit [70]. In addition, disseminated blood coagulation [71, 72] and oxidative stress [73–75] aggravated brain dysfunction of SE. MicroRNA (i.e., noncoding small RNA) involved in RNA silencing and posttranscriptional modification [76]. Besides nitric oxide (NO), lipid peroxidase, S100B protein [77], and the prion protein [78] may participate in SE.

3.4. Imbalance of synaptic transmissions on neurons

As a morphological study revealed that the neuronal spine was destabilized in a mouse model [79], neuronal environment may possibly be altered in SE. Actually, for other potent factors related to neurotransmission, norepinephrine [80], adrenergic system [81, 82], serotonergic

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system [83], acetylcholine [84–86], gamma-aminobutyric receptor A [87], N-methyl-D-aspartate receptor 2B [29], and brain neurovascular dysfunction [88] were involved in the pathogenesis of SE. In summary, sepsis leads to the aberrant conditions in the neuronal and/or glial environments and may result in the devastating symptoms in the pathogenesis of SE.

4. Brain activity measurements: from electrophysiology to imaging

4.1. Electrophysiology

Neurophysiological studies have uncovered the neuronal dysfunction in SE. Neurophysiologists have developed various experimental techniques to study neuronal cell activity. Neuronal activities recordings can be classified as follows: (1) single neuronal activity and (2) multiple neuronal activity. To record the single neuronal activity, there are techniques such as patch clamp recording and intracellular recording.

On the other hand, to record multiple neuronal activity, there are several established techniques. For example, there are field excitatory postsynaptic potentials (in vitro), local field potential (in vivo), and optical recording with voltage sensitive dye (in vitro and in vivo). For example, Kafa et al. reported reduced neuronal population activities in a rat model of SE [89], and Wang et al. also showed suppression of local field potentials during sensory stimulation in SE [30]. These findings are clearly similar to the clinical state of sensory dysfunction in septic patients [90]. It is useful to uncover the pathophysiological mechanism. These techniques are very powerful for studying the single neuron or several neurons in the local region of the brain. However, symptoms of SE are versatile with complicated diseases (e.g., stroke, edema, myopathy, etc.) [35, 91, 92]. Integrative analysis with multiple viewpoints is still required [93].

4.2. Brain imaging

Noninvasive measurement was sought to determine the pathological state and followed by prognosis of SE [94]. Several research reports suggest that electroencephalogram (EEG) that placed to the surface of head was useful to study brain dysfunction by various encephalitis and encephalopathy [95, 96]. In SE, for example, the EEG recordings revealed decreased amplitudes of EEG signals [97]. Using a rat model, EEG signals were attenuated [83]. In addition, child patient with coma showed 6-Hz burst firing pattern in SE [98]. Hence, EEG abnormality was found in the SE [99].

Why have these altered activity patterns due to brain dysfunction occurred? Functional magnetic resonance imaging (fMRI) has been used to capture the pathological state of brain cortex in SE [100]. Clinically, patients of SE showed cerebral infarction with multiple ischemic stroke and white matter lesions [13, 101]. Additionally, cerebral edema was reported [102]. Recently, brain atrophy within the regions including amygdala, hippocampus, basal ganglia, brainstem, thalamic, and cerebellar neurons was also shown in Ref. [103, 104]. Hence,

complicated symptoms, if they represent irreversible morphological alteration, have been found with fMRI. In addition to fMRI, positron emission tomography (PET) using 18 F-FDG was applied [105]; however, the application was limited. Conversely, reversible and time-dependent altered symptoms (e.g., neuronal transmission) cannot be determined with fMRI imaging (and PET) [106]. Because fMRI takes 10–30 min or more to capture a brain image with the high spatial resolution, it only determines the stable state of the pathology for SE. To overcome this weak point, we are currently focused on the noninvasive NIR imaging.

5. Near infrared (NIR) in vivo imaging

5.1. Probes

NIR imaging is a powerful tool for noninvasive in vivo imaging. Conventionally, visible light (400–700 nm) has been used for molecular fluorescent imaging in cellular dynamics [107, 108]. However, visible light is difficult to apply to deep-tissue imaging because of the robust light absorption and scattering by intrinsic chromophores (hemoglobin, melanin, flavin, etc.) and organelles (mitochondria and cytoskeleton). Autofluorescence from tissues (heart, skin, and brain) which is excited by NIR light (700–1400 nm) is much lower than that by excited visible light [109]. In addition, NIR light permeates tissues more than visible light (400–700 nm) (**Figure 2**). Therefore, the NIR light, especially 2nd optical window (1000–1400 nm), is currently expected to be applicable to noninvasive deep tissue imaging.

To label the target tissue, fluorescent probes are necessary. Compared to the visible light probes, NIR fluorescence probes are limited. For example, single-walled carbon nanotubes (SWNTs), Ag_2S quantum dots, PbS quantum dots, and rare-earth-doped nanocomposites are developed for 2nd optical windows for in vivo imaging (reviewed in Ref. [110]). We previously

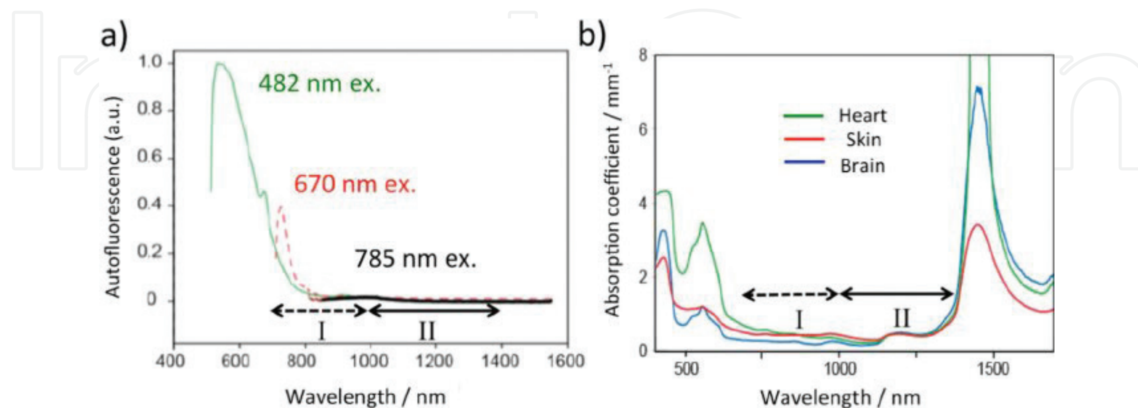

Figure 2. (a) Autofluorescence spectra of the dorsal side of a mouse body. The autofluorescence spectra were taken by excitation of 482, 670, and 785 nm. The dotted and solid arrows show the wavelength rage of 1st NIR optical window (I) and 2nd NIR optical window (II), respectively. (b) Absorption spectra of tissue slices of mouse skin, brain, and heart. Slice thickness of the skin, brain, and heart is 120, 100, and 200 μm, respectively. (Citation from Ref. [110]).

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compared these fluorescence probes in the same condition and found that PbS quantum dots were much brighter than other probes (**Figure 3**).

5.2. In vivo imaging

We applied PbS quantum dots (maximum fluorescence intensity: 1100 nm) from mouse tail vein and successfully recorded blood flow in the mouse head in a noninvasive manner [71] (**Figure 4**). The head of an anesthetized mouse was fixed on a stage of a microscope, and fluorescence was recorded through skin and skull (**Figure 4a**). The fluorescent intensity was recorded with InGaAs camera which is sensitive from 900–1600 nm. Soon after injection, brain blood vessels were visible on a mouse head (**Figure 4b**, right), and the picture was entirely similar to the image of blood vessels after scalp removal (**Figure 4c**, upper) and isolated brain (**Figure 4c**, lower). These findings suggest that the NIR in vivo imaging can visualize the brain blood flow non-invasively. If we would like to apply this method to the pathophysiology of SE, what is the target?

Brain blood vessels are aggravated in SE. Previous reports addressed that, using an animal model, cerebral microcirculation was reported to be impaired [111]. Disseminated intravascular coagulation (DIC) is an important pathological state of sepsis and worsening of DIC increases multiple organ dysfunction. Anticoagulant therapy was performed, however, its effect was limited. Repetitive administration of anticoagulant drug increases the rate of side effects such as thrombocytopenia [112] and bleeding [113]. To find the pathological state of DIC, we examined whether NIR in vivo imaging detect DIC in the septic brain as described in the next section.

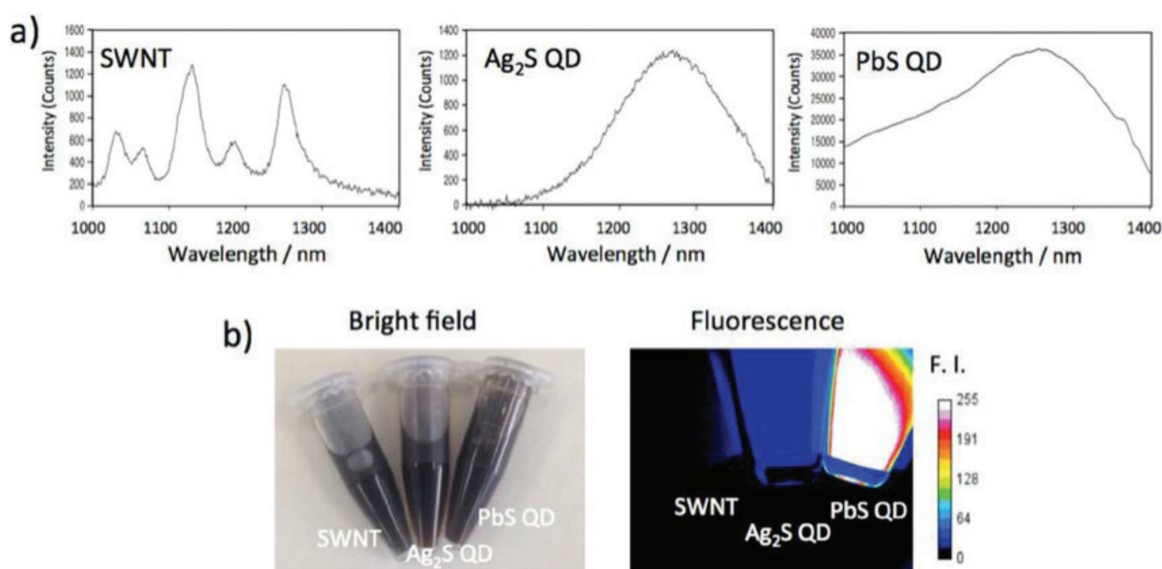

Figure 3. (a) Fluorescence spectra of nanomaterials that emit in the 2nd NIR window: SWNT, Ag_2S QD, and PbS QD. (b) Bright field and fluorescence images (>1000 nm) of SWNT, Ag_2S QD, and PbS QD. To compare the fluorescence brightness, absorbance at the excitation wavelength (720 nm) was adjusted to be the same value of 0.5 for SWNT, Ag_2S QD, and PbS QD. (Citation from Ref. [110]).

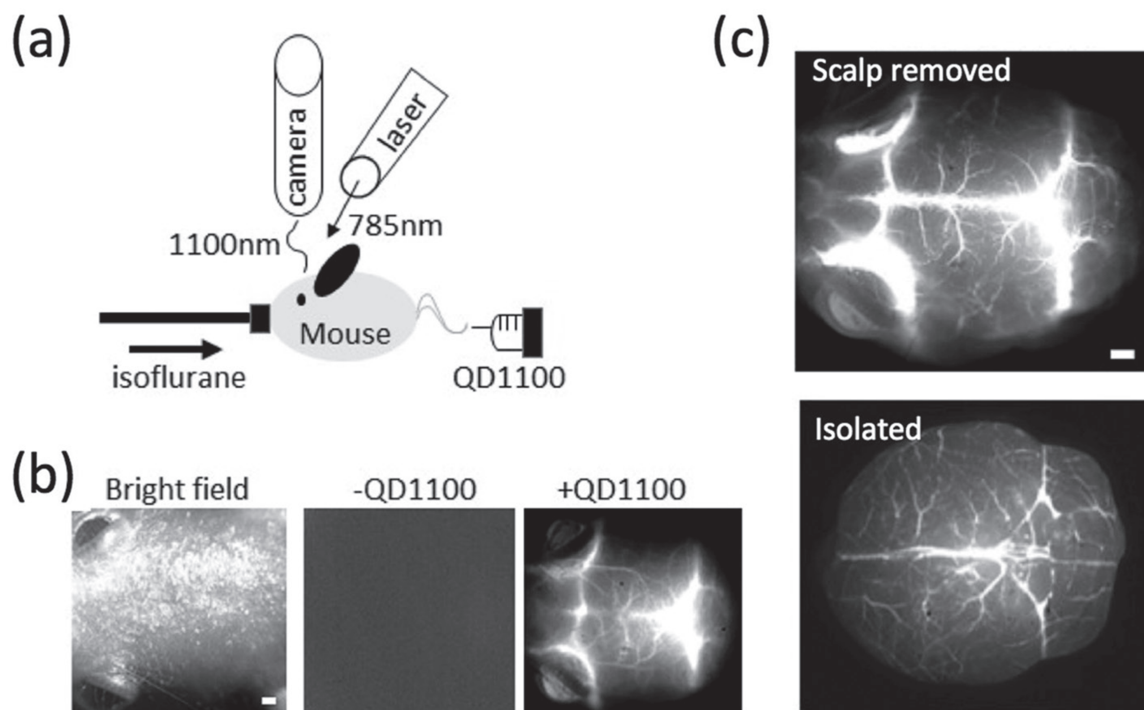

Figure 4. (a) Experimental setup for NIR fluorescence imaging of cerebral blood vessels. An anesthetized mouse was administered QD1100 in a caudal vein. An optical laser (785 nm wavelength) was used as an excitation light source, and NIR fluorescence was detected with an InGaAs camera; (b) imaging of a mouse head. Bright field image (left), NIR fluorescence image without QD administration (middle), and the NIR fluorescence image with QD administration (right). Scale bar: 1 mm; (c) NIR fluorescence images of cerebral blood vessels. Upper: fluorescence image after scalp removed, lower: fluorescence image after isolation. Scale bars: 1 mm. (Citation from Ref. [71]).

6. Application of NIR in vivo imaging to pathological analyses for septic encephalopathy

Next, we applied the NIR in vivo imaging to SE brain. To examine this, we studied whether DIC can be recorded with NIR imaging. **Figure 5** demonstrated lipopolysaccharide (LPS)-induced DIC. Eighteen hours after LPS, clots (arrowheads) can be recorded noninvasively (**Figure 5b**, middle). In the isolated brain, the number of clots remarkably increased in the SE brain (**Figure 6**). Conversely, the increased clots were similar to the control level in the presence of heparin (i.e., inhibitor of clots formation), suggesting that the NIR imaging can record DIC in SE brain.

What is the importance of these findings? In blood vessels of the brain, tissue factor activation including thrombin and fibrinogen which enhanced blood clot formation was occurred [114, 115], and this pathology finally led to multiple organ (e.g., lung, liver, kidney, and brain, etc.) dysfunction [116]. However, it has been difficult to visualize the pathological state of DIC because of a lack of an effective biomarker [117]. Our present findings developed a novel approach to analyze the pathological state of brain blood vessels in SE.

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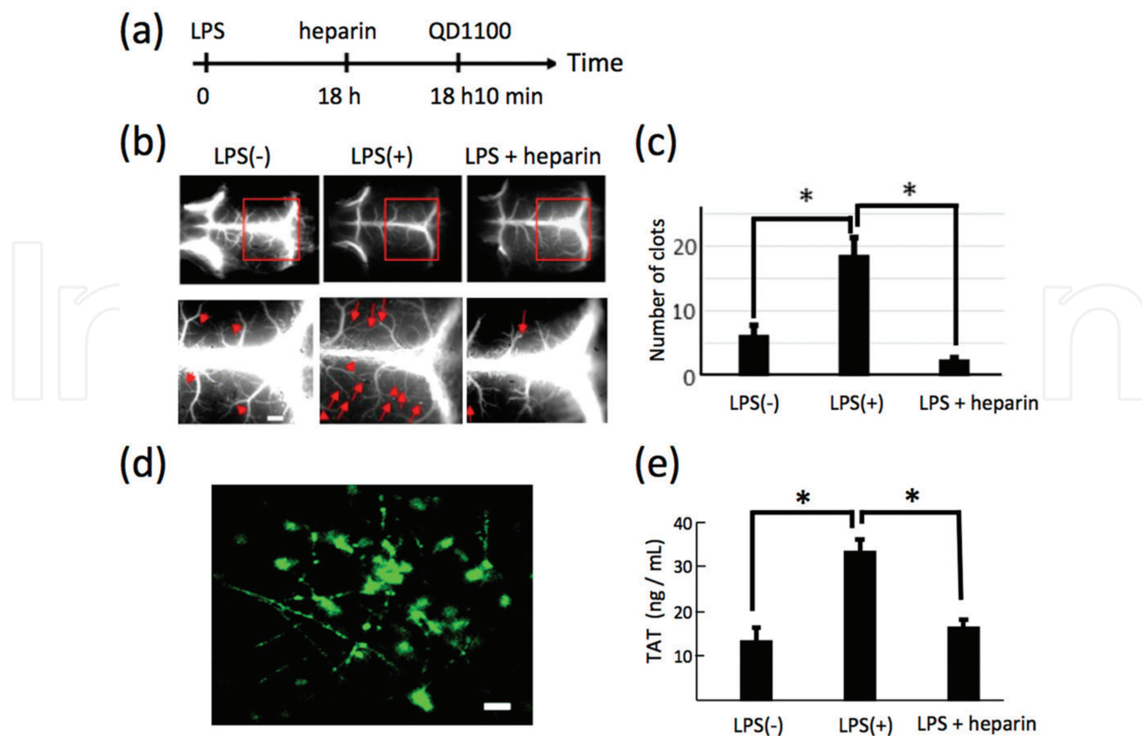

Figure 5. (a) Time course of experimental procedure for lipopolysaccharide (LPS) and heparin administration; (b) NIR fluorescence images (>1000 nm) of cerebral blood vessels before and after administration of LPS (LPS (−) and LPS (+)), and the image following additional administration of heparin (LPS + heparin) with scalp removed. Lower panel shows the magnification of the images shown by red rectangles. Arrowheads show clots. Scale bars: 1 mm; (c) statistical analyses of the clots in the cerebral vessels. *: $p < 0.05$, number of mice: LPS (−): $n = 5$, LPS (+): $n = 5$, LPS + heparin: $n = 3$; (d) immunofluorescence staining of LPS-treated cerebral blood vessels, where antifibrinogen antibody (Alexa Fluor 488) was used for staining of fibrinogen. Fibrinogen helps the formation of blood clots. Scale bar: 10 μm; (e) ELISA assays for thrombin–antithrombin complex (TAT) in blood plasma. *: $p < 0.05$, number of mice: LPS (−): $n = 5$, LPS (+): $n = 5$, LPS + heparin: $n = 3$. (Citation from Ref. [71]).

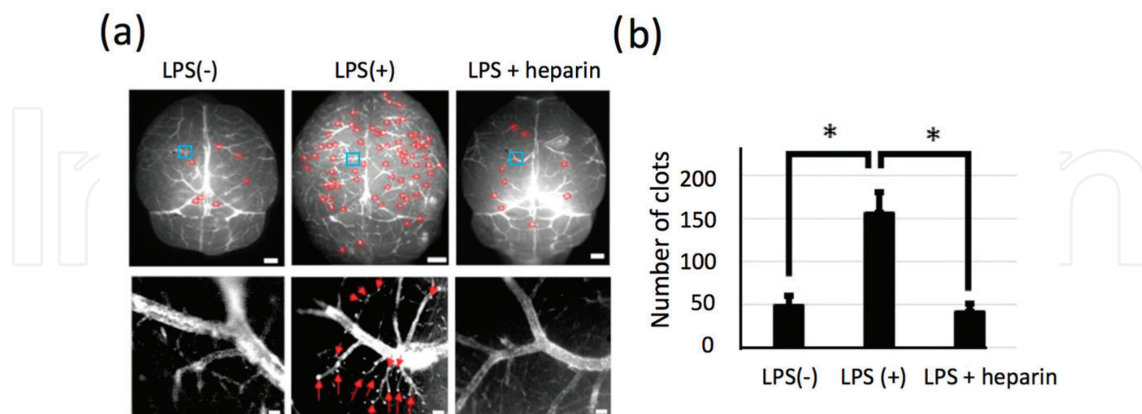

Figure 6. (a) Upper panel: NIR fluorescence images (>1000 nm) of cerebral blood vessels of isolated mouse brains. Left: LPS (−), Middle: LPS (+), Right: LPS + heparin. Red circles: clots. Blue squares: region of interests for the magnified views of lower panels. Scale bars: 1 mm. Lower panel: magnified NIR fluorescence image of cerebral blood vessels at the bregma. Red arrows: clots. Scale bars: 100 μm; (b) Number of clots for each mouse. *: $p < 0.05$, number of mice: LPS (−): $n = 5$, LPS (+): $n = 5$, LPS + heparin: $n = 4$. (Citation from Ref. [71]).

7. Future prospect

In this chapter, we introduce the application of NIR in vivo imaging to SE. Currently, imaging technology is confronted with a turning point. Although there are several noninvasive imaging technologies (PET, MRI, etc.), NIR noninvasive imaging can possibly record the faster time-dependent changes of pathological state in SE, though further developments of the imaging algorithm are required. In addition, the NIR imaging can label the distinct proteins by several specific antibodies and perform the multiple molecular in vivo imaging. Therefore, using the biomarker for SE, we may be able to visualize the novel pathophysiological mechanisms of SE.

Finally, in addition to our challenges, other candidate biomarkers which employ correlation to the pathological state of SE are recently addressed: S100β (i.e., astrocyte-secreting protein) [77, 118–120], free radicals [121, 122], ascorbate [123–125], and various neuropeptides [126]. In addition, adult neurogenesis was induced in a rat model of SE and the neurogenesis marker (e.g., 5-bromo-2′-deoxyuridine) might be useful [127]. In conclusion, these multidisciplinary approaches may overcome the pathophysiology and lead to innovative therapeutics for SE.

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