Pathophysiology of Ischemic Stroke

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Here, the classification and pathophysiology of ischemic stroke will be discussed in detail. Ischemic stroke is often classified for academic purposes, but there is actually a very practical reason for its classification. Ischemic stroke is a clinical syndrome, which develops not with a single cause but with multiple causes. Ischemic stroke with a different cause would have a different clinical developmental pattern, and more decisively, the medicine and therapy for treatment and prevention vary. Thus, its proper confirmation would great influence the patient's prognosis. In this chapter, the classification of ischemic stroke and the latest knowledge on the pathophysiology related to it will be presented.

1.1 Classification of Ischemic Stroke

Stroke is classified for various purposes. It is often classified for academic purposes, to describe the characteristics of the patients included in a clinical study or to classify the patient group according to their characteristics, but the clinical purpose of its classification—to determine the appropriate treatment plan for a stroke patient—is also very important. Most of the stroke registry studies that have been conducted so far revealed that 25–40% of all stroke patients could not find the cause of their stroke [1]. The frequency varies depending on the quality, completeness, and examination timing of the diagnostic tests for stroke etiology. The stroke whose cause is not known is called "stroke of unknown cause, or cryptogenic stroke." Moreover, there are many cases where it has more than two possible causes and it is difficult to determine which of the causes is the real one (e.g., a case accompanied by atrial fibrillation and significant stenosis of the internal carotid artery associated with the location of cerebral infarction).

1.1.1 Stroke Data Bank Subtype Classification

A solid classification system for ischemic stroke did not exist previously, but since the advent of computed tomography (CT) opened an era of neuroimaging, classification methods have been suggested. Stroke Data Bank Subtype Classification is a method that was initially derived from the stroke register protocol of Harvard University and that classifies stroke into the following five types indicated in the Stroke Data Bank established by the National Institute of Neurological Disorders and Stroke (NINDS): (1) brain hemorrhage, (2) brain infarction (atherothrombotic and tandem arterial pathological abnormalities), (3) cardioembolic stroke,

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(4) lacunar stroke, and (5) stroke from rare causes or with an undetermined etiology.

The definition of atherothrombotic brain infarction in this classification is more than 90% stenosis in the relevant cerebral artery, which is very limited. For this reason, the proportion of patients diagnosed with atherothrombotic brain infarction was underestimated, and as such, the cases of stroke with an undetermined etiology increased, representing approximately 40% of all the stroke cases. In other words, in this classification method, the etiology of about half of all stroke patients could not be identified. Additionally, the definition of lacunar stroke was too broad, based only on the clinical symptoms and signs, which was inevitable because at the time of establishment of such classification method there were no brain imaging techniques such as CT angiography or MR angiography that could determine the pathology of the intracranial artery.

1.1.2 Oxfordshire Community Stroke Project Subtype Classification

Oxfordshire Community Stroke Project (OCSP) was originally suggested to identify the characteristics of the subjects in epidemiology studies of Oxfordshire community (Table 1.1). At the time, the OCSP researchers were forced to exert efforts to meet the standard of diagnostic tests available in the British public healthcare system because all the stroke patients in the UK are treated by primary care physicians. Besides the clinical findings, CT is the best examination method among others, and there was no way at that time to confirm the problem in the brain vessel itself or the presence of a heart disease. Therefore, the OCSP researchers chose a method of classifying patients depending on the site and size of their ischemic stroke on a clinical basis. As the size and location of ischemic stroke are not determined by the cause of stroke, however, even a patient whose stroke is classified as lacunar stroke has a possibility of having stenosis in the M1 portion of middle cerebral artery or atrial fibrillation, but there is no way to figure this out in most cases. In early stage of ischemic stroke, lesions are not clearly shown on the CT image in many cases, and in such cases, the patients' stroke is classified depending only on the clinical findings. Thus, approximately 20–30% of stroke cases are known to have been misclassified. This classification method, however, depends only on the location and size of the ischemic stroke based simply on the clinical findings and CT; as such, it

Table 1.1 OSCP classification

Type of infarct	Diagnosis
Cerebral infarction	If a CT scan performed within 28 days of symptom onset shows an area of low attenuation, no relevant abnormality or an area of irregular high attenuation within a larger area of low attenuation (i.e., an area of hemorrhagic infarction) or if a necropsy examination shows an area of cerebral infarction (pale or hemorrhagic) in a region compatible with the clinical signs and symptoms
Lacunar infarct (LACI)	One of the four classic clinical lacunar syndromes. Patients with faciobrachial or brachiocrural deficits are included, but more restricted deficits are not
Total anterior circulation infarct (TACI)	Combination of new higher cerebral dysfunction (e.g., dysphasia, dyscalculia, visuospatial disorders), homonymous visual field defect, and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg. If the conscious level is impaired and formal testing of higher cerebral function or the visual fields is not possible, a deficit is assumed
Partial anterior circulation infarct (PACI)	Only two of the three components of the TACI syndrome, with higher dysfunction alone or with a motor/sensory deficit more restricted than those classified as LACI (e.g., confined to one limb or to the face and hand but not the whole arm)
Posterior circulation infarcts (POCI)	Any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit, bilateral motor and/or sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (i.e., ataxic hemiparesis), or isolated homonymous visual field defect

OCSP Oxfordshire Community Stroke Project

has advantages in that the classification is easy and almost all stroke cases can be classified. The classification is so easy that communication between the physicians and the interobserver reliability is very high. Also, as the prognosis of a patient is determined by the initial severity of the stroke, considerable predictions can be made based on this classification method, even without knowing the cause of the ischemic stroke.

1.1.3 Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Subtype Classification

Since 1993, almost all clinical researchers in the world have used the classification system suggested by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) clinical researchers (Table 1.2). The original purpose of this classification system was to analyze the effect of danaparoid in the subtypes of strokes. The TOAST researchers classified stroke initially into 11 categories, but they later compressed these categories into five groups. This is a classification system whose internal validity can be increased if the researchers follow the pre-planned algorithm, and accuracy in diagnosis may improve if there are more than two evaluators. Lacunar infarction is defined by the clinical symptoms and the size of the ischemic stroke. In this case, if significant stenosis in the M1 portion of middle cerebral artery is not detected because thorough examination of the cerebral artery has not been done, the ischemic stroke caused by large-artery atherothrombosis is likely to be misclassified as lacunar infarction. In addition, the causes of cardioembolism consist of high- and medium-risk factors, and among the medium-risk factors are many factors that are too ambiguous to be considered a cause of cardioembolism, such as patent foramen ovale. Therefore, there is a possibility for a stroke patient with a medium-risk factor, whose intracranial and extracranial arteries had not been thoroughly examined, to be misclassified as cardioembolism. Moreover, the cases of ischemic stroke with an undetermined

Table 1.2 TOAST classification

Type of infarct	Diagnosis
Large-artery atherosclerosis	Clinical evidence of cortical, subcortical, brain stem, or cerebellar dysfunction with more than 50% lesion or occlusion in an extracranial or intracranial vessel in the distribution of an infarct larger than 1.5 cm by CT or MRI. This diagnosis cannot be made if arterial studies show no evidence of pathology or if there is reasonable suggestion by history or studies that another mechanism is possible
Cardioembolism (high risk/medium risk)	Clinical evidence of cortical, subcortical, brain stem, or cerebellar dysfunction with a lesion size larger than 1.5 cm on CT or MRI and the presence of at least one high-risk (e.g., atrial fibrillation or mechanical heart valve) or medium-risk cardiac pathology (e.g., lone atrial fibrillation or patent foramen ovale) on diagnostic studies, electrocardiogram, rhythm strip, 24-h cardiac monitoring, and transthoracic or transesophageal echocardiography. Evidence of transient ischemic attacks or strokes in more than one vascular territory or of systemic emboli supports the diagnosis. Finally, other categories (large artery, small artery) must be excluded
Small-vessel occlusion (lacunar)	A lacunar syndrome (pure motor, sensorimotor, pure sensory, ataxia hemiparesis, dysarthria-clumsy hand) with normal CT or MRI or a lesion smaller than 1.5 cm on CT or MRI in the territories supplied by small-vessel penetrators. Large-artery and cardiac sources must be excluded
Stroke of other determined etiologies	Stroke caused by nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders and other rare causes of stroke after diagnostic testing. Other categories must be excluded
Stroke of undetermined etiology (cryptogenic)	This diagnosis is made if two or more etiologies of stroke are possible, a complete evaluation reveals no possible source, or the patient had an incomplete evaluation

TOAST Trial of Org 10172 in Acute Stroke Treatment

cause include both the cases where the stroke has two or more distinct causes or where the cause of the stroke is not found even after sufficient examination. For example, in a case where the patient has more than 50% vascular stenosis and atrial fibrillation, the stroke is in principle classified as ischemic stroke with an undetermined cause. Even all the cases where the physician or researcher can make a diagnosis based on a strong hunch are in principle classified as ischemic stroke with an undetermined cause, and consequently, the proportion of cases of ischemic stroke with an undetermined cause is exaggerated.

1.1.4 The Path of Stroke Classification

Stroke classification does not exist simply for clinical research purposes. It should be well applied to usual patient care, and well used for patients' early diagnosis, for prognosis determination, and for the medication for stroke prevention. The classification made using an expensive equipment or examination method may pose a problem in the country's public health, but if classification is simply made based only on the clinical findings and CT image obtained, there are bound to be too many errors. Each country needs to establish the optimal classification system employing appropriate tests that fit the public health characteristics of the patients in the country.

1.2 Thrombus Formation According to the Stroke Etiology

Occlusion of the blood vessels, a cause of ischemic stroke, is usually caused by a thrombus (or a blood clot). Therefore, the core of stroke pathophysiology is to understand the process of thrombus formation. According to the ischemic stroke classification, a thrombus with a different appearance may develop. Thus, the basic process of thrombus generation must be understood. Thrombi largely consist of two components as an end product of the blood coagulation process: a platelet plug and a fibrin protein cross-linked like a mesh. In general, the condition in which thrombi develop is known as "Virchow's triad," and its description is as follows: (1) damage in the vascular endothelial cell (trauma or arteriosclerosis), (2) abnormal blood flow (loss of laminar flow due to blood stasis in the vein or turbulence in the artery), and (3) hypercoagulability state. The thrombi caused by these reasons are classified into the following depending on the component: white thrombus, whose major components are platelets, or red thrombus, whose major components are red blood cells (Fig. 1.1). Both types of thrombus may develop in ischemic stroke. Depending on the type of thrombus that is the major cause of stroke, the patient's early progression, the effect on the acute-phase treatment, the prognosis, and the secondary prevention vary. Thus, most of all, it is important to identify the

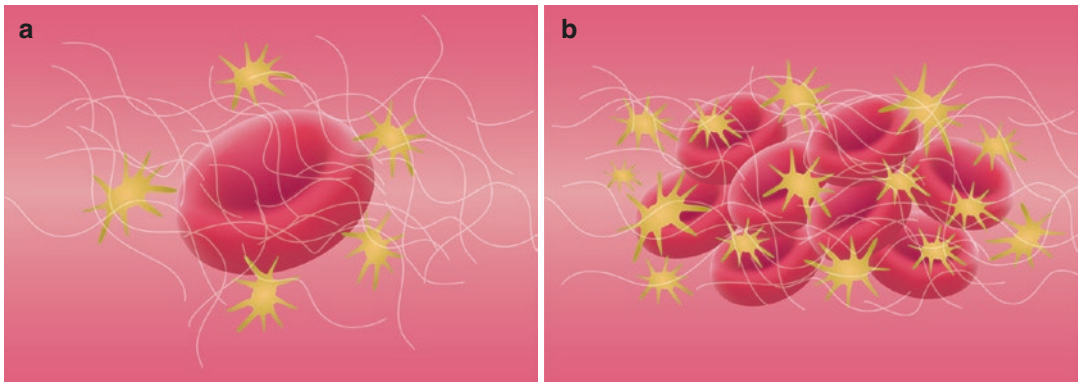

Fig. 1.1 Schematic figures of white thrombi (**a**) and red thrombi (**b**)

onset mechanism, components, and important factors of the thrombus for the appropriate diagnosis and treatment of ischemic stroke patients.

1.2.1 Formation of Platelet Thrombus

In the maintenance of the vascular system and homeostasis, the endothelial cells, the collagen in the subendothelial tissue, and the tissue factor (TF) are important. In particular, the endothelial cells form tunica intima and have three thromboregulators inhibiting thrombus formation: nitric oxide, prostacyclin, and ectonucleotidase CD39 [2].

1.2.1.1 Two Independent Pathways for Platelet Activation

One is the collagen pathway, and the other is the TF pathway (Fig. 1.2). If the vessel wall is disrupted, the collagen and TF are exposed to the blood, and thrombus formation starts. Collagen facilitates platelet coagulation and activation, while TF initiates thrombin formation, activates the platelets, and changes fibrinogen into fibrin. In the two pathways, either of the two can be dominantly activated depending on the situation, but the result is the same in that the platelets are activated.

With regard to the collagen pathway, platelet adhesion occurs through the interaction between the exposed collagen and the glycoprotein VI of the platelet and through the interaction between the von Willebrand factor attached to the collagen and the glycoprotein Ib-V-IX of the platelet. Glycoprotein VI acts as the most important factor in early platelet activation and platelet granule secretion. The platelet activation here is irrelevant to thrombin.

TF causes the formation of the TF pathway, the second most important pathway in early platelet activation. The platelet activation here is irrelevant to the major components of the collagen pathway, the rupture of the vascular endothelial cells, the von Willebrand factor, and glycoprotein VI. Originally, TF has two forms. It is present on the vessel wall in an inactivated or encryptic form, or in an activated form inside the vessel wall. The inactivated TF is

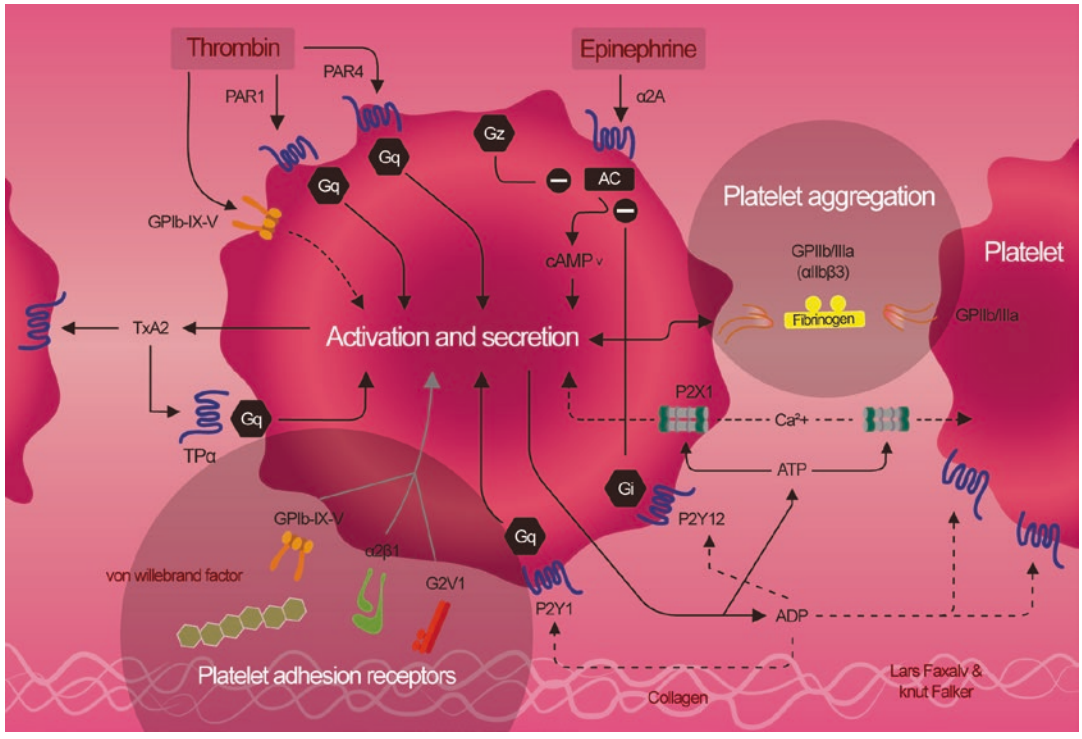

Fig. 1.2 Mechanism of platelet activation

activated by protein disulfide isomerase, and such TF forms a complex with factor VIIa, and the complex produces thrombin along the proteolysis pathway while sequentially activating factor IX. Thrombin activates the platelets while decomposing the protease-activated receptor 4 (Par 4 in mouse; Par 1 in human) on the surfaces of the platelets. As a result, adenosine diphosphate (ADP), serotonin, and thromboxane A2 are secreted from the activated platelets. The secreted substances amplify the signal for thrombin formation while activating different platelets sequentially.

1.2.1.2 Propagation of Thrombi Composed of Platelets

The integrin αIIbβ3 of a platelet plays the role of drawing platelet-platelet and platelet-thrombus interactions while being activated. For αIIbβ3 activation, protein disulfide isomerase is necessary. The activation of a platelet attached to the damaged vessel wall promotes a structural change of αIIbβ3 and consequently makes the ligand of αIIbβ3 increase the affinity with fibrinogen or the von Willebrand factor. At a small shear rate, the affinity with fibrinogen is more important, while at a high shear rate, the affinity with the von Willebrand factor is relatively more important. This does not mean, however, that fibrinogen and the von Willebrand factor are absolutely necessary for thrombus formation in this situation. An activated platelet secretes alpha and dense granules. These secretions play a crucial role in thrombus formation. The alpha granule contains various proteins, and the dense granule contains ADP and calcium ion. The ADP secreted through a dense granule facilitates platelet activation more by attaching to the P2Y1 and P2Y12 receptors of the platelet.

1.2.2 Blood Coagulation

1.2.2.1 Contact Activation Pathway (Intrinsic Pathway)

The contact activation pathway begins with the initial complex composition by high-molecular-weight kininogen (HMWK), prekallikrein, and factor XII (Hageman factor) on collagen (Fig. 1.3). As prekallikrein changes to kallikrein, factor XII is activated into XIIa. XIIa changes factor XI into XIa, while XIa changes factor IX into IXa. IXa makes up a tenase complex with a cofactor, factor VIIIa, and this complex activates factor X to Xa. The contact activation pathway in blood coagulation is very strong for coagulation in in vitro studies, but it is not necessary for starting blood coagulation in in vivo studies. The activation of factor XII is very important because it is the starting point of the formation of the contact pathway, and the absence of this factor has been confirmed to mean a very prolonged partial thromboplastin time. Strangely, however, it is not true that patients who do not have this factor have bleeding disorders. Therefore, the importance of factors XII and XI is slightly vague. As it has been confirmed that both factors are associated with thrombus formation in mice, their roles in different biological species may be different. In humans, the pathway is more likely to be associated with inflammation or a congenital immune system rather than with coagulation.

1.2.2.2 TF Pathway (Extrinsic Pathway)

The TF pathway plays the role of leading an "explosive increase of thrombin," its most important component, through a feedback mechanism in the entire coagulation pathway. As mentioned earlier, TF is a membrane protein with very complex roles. It is mainly expressed in the fibroblast, in the pericyte in the outer membrane of a vessel, and in the smooth muscle cell of the vessel wall and is often expressed in other cells not related to the blood vessels. TF interacts with several less than 1,000-nm microparticles existing in the blood. During thrombus formation, the platelet is attached to the vessel wall and expresses adhesion molecules called P-selectin while being activated. P-selectin is connected with the microparticles, expressing a receptor called P-selectin glycoprotein ligand 1 (PSGL-1), and causes the microparticles expressing the TF derived from monocytes to be captured in the thrombus. Like this, the TF derived from the blood plays an important role in fibrin extension within the thrombus. As TF performs activities related to blood coagulation only in the activated status, for the inactivated TF (in the latent or encrypted form) existing in the vascular endothelial cells to participate in blood

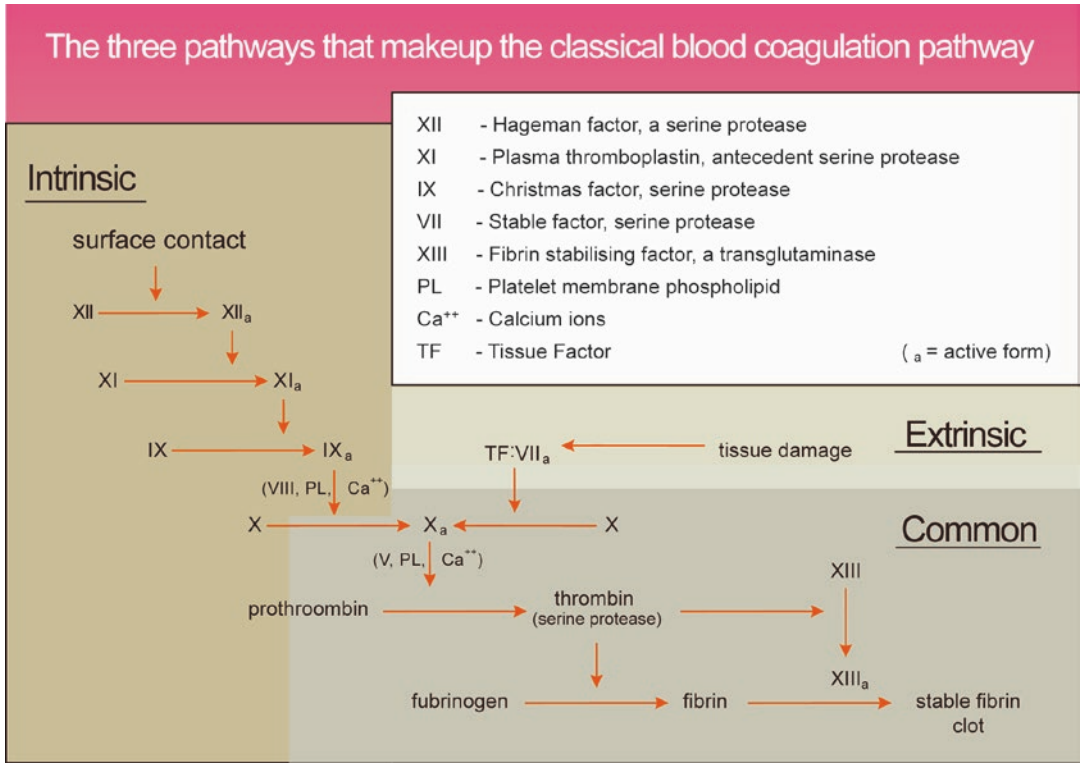

Fig. 1.3 Cascades of clotting factor activation: contact activation pathway (or intrinsic pathway), tissue factor pathway (or extrinsic pathway), and common pathway

coagulation, the activation process is required. The TF activation mechanism is not clear in molecular biology, but it is thought that as the disulfide bonds in the cysteine within the TF protein are separated, it is activated. These bonds are separated by the aforementioned protein disulfide isomerase and are isolated from the activated endothelial cells or platelets. Therefore, protein disulfide isomerase is involved in both fibrin and platelet thrombus formation.

Among the many blood coagulation factors, the amount of factor VIIa in the blood is greater than those of the other coagulation factors. Factor VII is activated by thrombin, XIa, XII, and Xa, and if the blood vessels are damaged, factor VIIa enters the fibroblasts or monocytes containing TF and makes a complex by binding with TF. This complex activates factors IX and X. The activation of X by a complex can be immediately inhibited by the tissue factor pathway inhibitor (TFPI). Factor Xa and its cofactor, factor Va, form a prothrombinase complex, which converts prothrombin into thrombin. Thrombin affects various coagulation factors, and factors V and VIII are applied to this case. As mentioned earlier, the activated factor VIIIa here acts as a cofactor of factor IXa and makes a tenase complex. As this process is repeated, the thrombin formation process is amplified.

1.2.2.3 Common Pathway

The aforementioned pathway is in fact a result from the laboratory, which measures what is activated by the isolated surface (contact activation pathway) or thromboplastin (a complex of tissue factor and phospholipid). Actually, thrombin exists from the time a platelet is initially coagulated and carries out many functions besides the simple conversion of fibrinogen into fibrin. Thus, it is the most important coagulation factor in blood coagulation. With regard to the function of thrombin, simply put, it activates

factors VIII and V, and if thrombomodulin exists, it also activates protein C. Here, the activated protein C inhibits factors VIII and V and compromises the blood coagulation. In addition, by activating factor XIII, it plays the role of cross-linking fibrin monomers into polymers. The common pathway serves to maintain the coagulation trend by continuing to activate factors VIII and IX until they are suppressed by the anticoagulation mechanisms.

1.2.2.4 Cofactor and Modulator

The following components play an important role in maintaining the homeostasis as a whole with the blood coagulation cofactors and modulators. Here, two cofactors and five modulators will be mentioned.

Cofactor

The cofactors include calcium, phospholipid, and vitamin K. Phospholipid, as a component of calcium and the platelet membrane, acts as a cofactor in the function of the tenase and prothrombinase complexes. Besides this, calcium is reported to have a role in the activation of other coagulation factors. Vitamin K is an essential element for an enzyme called hepatic gamma-glutamyl carboxylase attaching a carboxyl group to the glutamic acid residues of factors II, VII, IX, and X and proteins C, S, and Z. In this process, vitamin K itself is oxidized. An enzyme called vitamin K epoxide reductase (VKORC) reverts vitamin K to the activated status. As VKORC is a target substance of warfarin, it is a very important enzyme pharmacologically. By blocking VKORC, warfarin causes vitamin K deficiency and blocks the activation of the coagulation factors.

Modulator

The modulators include protein C, antithrombin, tissue factor pathway inhibitor (TFPI), plasmin, and prostacyclin (PGI2). Protein C is a major anticoagulant in the body and is activated by thrombin, to which the cell surface protein, thrombomodulin, is bonded. Activated protein C decomposes and inactivates factors Va and VIIIa with a cofactor, protein S, and phospholipid. Protein C or S deficiency leads to various forms of thrombosis, including cerebral infarction. Antithrombin is a serine protease inhibitor (serpin) that decomposes thrombin and factors IXa, Xa, XIa, and XIIa, which are serine proteases. It is always in the activated status, and if heparan sulfate exists or if heparin is injected from outside, the effect is enhanced. Also, if there is a deficiency in it, various forms of thrombosis, including cerebral infarction, may occur. As mentioned earlier, the tissue factor pathway inhibitor (TFPI) limits the action of TF. In the liver, plasmin develops through the decomposition of plasminogen. The process is catalyzed by the tissue plasminogen activator (t-PA), which is synthesized and secreted by the vascular endothelial cells. Plasmin decomposes fibrin into the fibrin degradation product (FDP) and inhibits excessive fibrin formation. For the initial treatment of ischemic stroke, the method of injecting recombinant t-PA for thrombolysis is authorized worldwide and is used extensively. Prostacyclin (PGI2) is secreted at the endothelial cells and activates the Gs-protein-linked receptor of the platelet. It sequentially activates adenylyl cyclase and increases the cAMP synthesis. cAMP lowers the calcium level in the cell, suppresses platelet activation, and inhibits the secretion of granules that induce the activation of the secondary platelet/coagulation factor.

1.3 Mechanism of Vascular Occlusion Causing Ischemic Stroke

The classification of ischemic stroke and the mechanisms of thrombus development in the blood have been presented in detail. The reason for the occurrence of acute ischemic stroke, however, is actually that the blood vessel governing the local cerebral region is blocked in an instant. As a lesion that may cause ischemic stroke exists in the blood vessel itself in many cases, it cannot merely be explained with the onset mechanism of thrombus in the blood, and the actual mechanism of occlusion needs to be logically understood. The reason that the blood vessels are occluded is explained differently depending on the TOAST

classification, and here, the mechanism of the occurrence of acute occlusion of the blood vessels will be explained in accordance with the classification. Only the mechanisms in large-artery atherosclerosis, small-vessel occlusion, and cardioembolism, however, which account for approximately 70% of the ischemic stroke cases, will be described herein, and the mechanisms of occlusion in other rare etiologies will not be mentioned here.

1.3.1 Mechanism of Occlusion in Large-Artery Atherosclerosis

Atherosclerosis is a chronic inflammatory disease developed by innate and adaptive immunity with the lipids in the artery wall as major components (Fig. 1.4). At first, it is accompanied by dysfunction in the vascular endothelial cells, and as the blood vessels are exposed to excessive lipids (low-density lipoprotein, LDL), the lipids start to accumulate under the intima. If a person is frequently exposed to different risk factors (hypertension, diabetes, smoking, infection, stress, etc.), the damage in endothelial cells becomes severe, and due to the damaged endothelial cells, more LDL cholesterol particles accumulate in the extracellular matrix (ECM), which becomes the place where the damage caused by the oxidation and decomposition enzymes most frequently occurs. The modified LDL activates various inflammatory responses, and its major mechanism is the infiltration of monocytes, which plays the most important role in innate immunity. Also, it is known that adaptive immunity, including the helper T cells (Th1 and Th2) and the antibodies, plays a significant role in the expansion of arteriosclerosis. If monocytes infiltrate and reach the subendothelial region, they are differentiated into macrophage by the macrophage colony-stimulating factor. Macrophage can be differentiated into subtypes with various types and functions according to the environment around it, and such

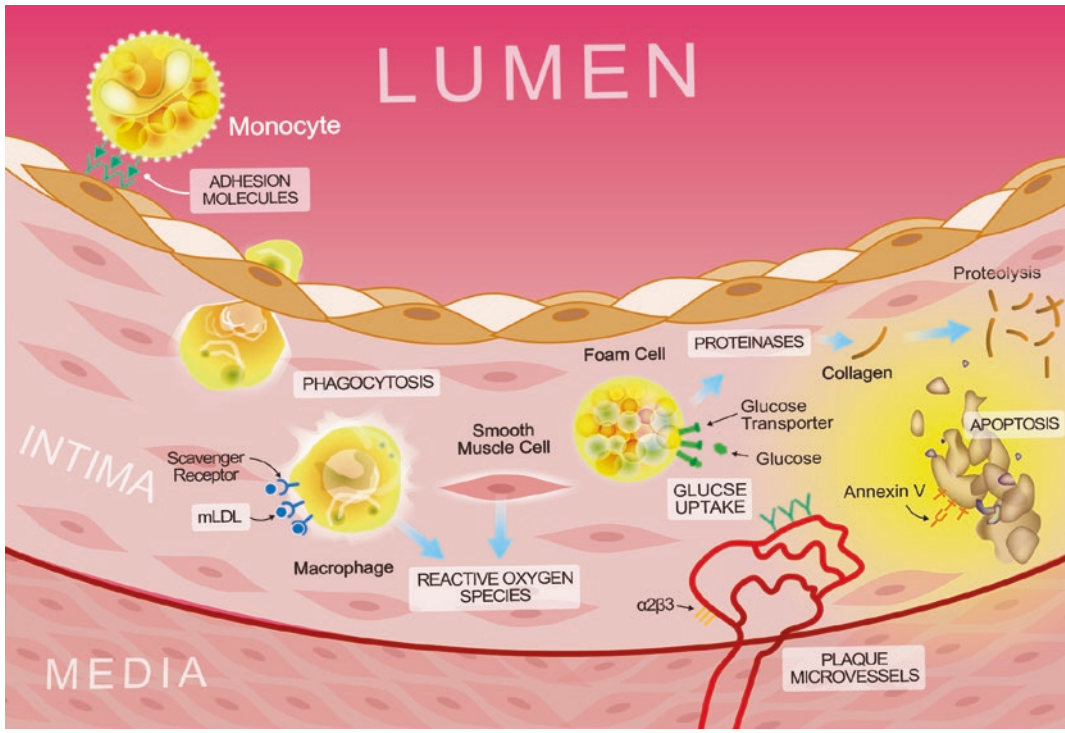

Fig. 1.4 Progression of atherosclerotic lesion (shown as time sequence from left to right)

a process is called "polarization." There are two macrophage subtypes that can be very clearly distinguished from each other depending on the atherosclerosis process, which are known as M1 and M2 (Fig. 1.5). A differentiated macrophage goes through a lipid-containing macrophage while expressing a surface pattern recognition receptor well receiving the modified LDL and changes to a foam cell. As the foam cell secretes cytokines and growth factors, lesions progress, and the vascular smooth muscle cell (VSMC) moves from the media to the intima, where ECM materials, which are important in fibrous cap formation, are produced. In fact, many lipid-containing macrophages are removed by M2 macrophage through the process called "efferocytosis" after initially going through the process of apoptosis. Nevertheless, as macrophage excessively takes apoptosis cells, the endoplasmic reticulum is stressed. Consequently, defects in efferocytosis occur, which isolates the death of the macrophage and lipids, the inflammatory factor, the coagulation factor such as TF, and the matrix metalloproteinases (MMPs). MMP induces the rupture of the atherosclerotic plaque while decomposing the ECM scaffold such as the fibrous cap. The plaque vulnerability is exacerbated as the infiltration of VSMC becomes smaller, and more immature and leaky microvessels occur in the core necrotic plaque.

1.3.1.1 Classification of Atherosclerotic Plaque

WHO classified and reported the atherosclerotic plaque for the first time in 1958, and the four classes are as follows: fatty streak, atheroma, fibrous plaque, and complicated lesion. In the mid-1990s, the American Heart Association (AHA) recommended a new classification standard for the atherosclerotic plaque, and later, several researchers refined the classification system as it was confirmed that plaque erosion could also cause coronary thrombosis [3–5]. Table 1.3 and Fig. 1.6 present the current classification system of coronary atherosclerotic plaque based on this. The classification system of atherosclerotic

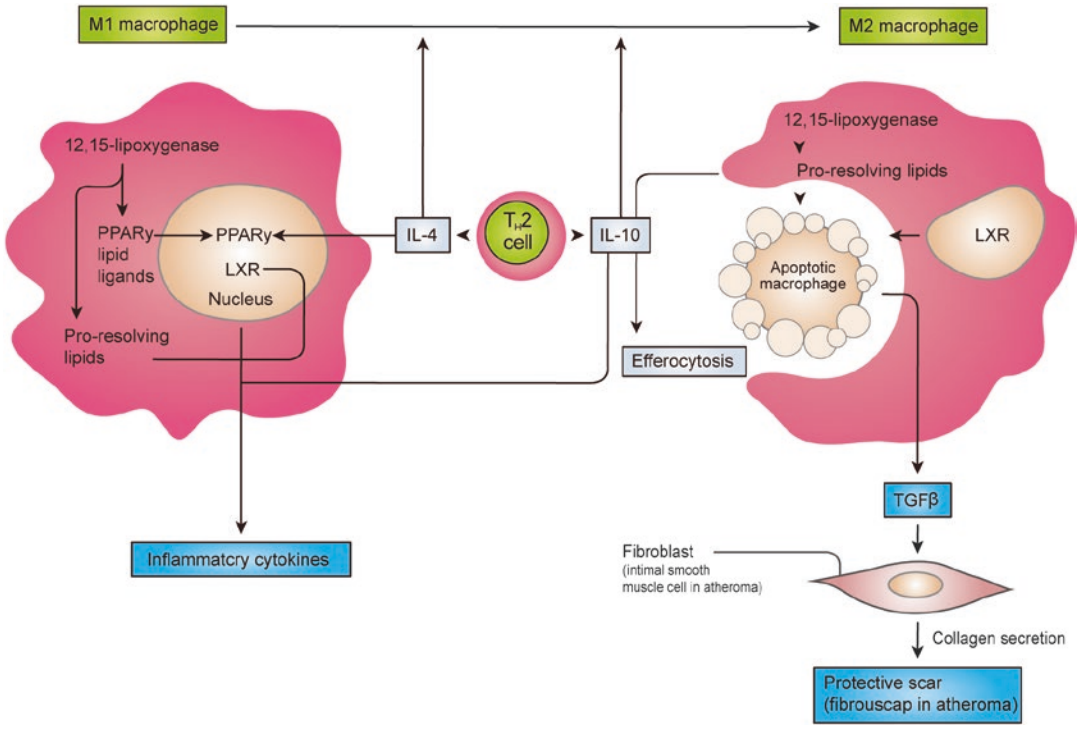

Fig. 1.5 M1 and M2 subtypes of macrophage with differential functions according to atherosclerotic stage

Table 1.3 Classification of atherosclerotic lesion

Type of lesion	Subtype of lesion	Morphological description
Nonatherosclerotic intimal lesions	Intimal thickening	Natural accumulation of smooth muscle cells in the absence of lipid, macrophage foam cells, and thrombosis
	Intimal xanthoma	Superficial accumulation of foam cells without a necrotic core, fibrous cap, or thrombosis
Progressive atherosclerotic lesions	Pathological intimal thickening	Plaque rich in smooth muscle cells, with hyaluronan and proteoglycan matrix and focal accumulation of extracellular lipid. Absence of thrombosis
	Fibroatheroma	During early necrosis: focal macrophage infiltration into areas of lipid pools with an overlying fibrous cap. During late necrosis: loss of matrix and extensive cellular debris with an overlying fibrous cap. With or without calcification. Absence of thrombosis
	Intraplaque hemorrhage or plaque fissure	Large necrotic core (size >10% of plaque area) with hemorrhage, and plaque area shows the presence of angiogenesis. Necrotic core communicates with the lumen through a fissure. Minimal tear without obvious thrombus
	Thin-cap fibroatheroma	A thin, fibrous cap (<65 μm) infiltrated by macrophages and lymphocytes, with rare or no smooth muscle cells and relatively large underlying necrotic core (>10% of plaque area). Intraplaque hemorrhage and/or fibrin might be present. Absence of thrombosis
Lesions with acute thrombi	Plaque rupture	Thin-cap fibroatheroma with cap disruption. Thrombosis is present and might or might not be occlusive. The luminal thrombus communicates with the underlying necrotic core
	Plaque erosion	Can occur on pathological intimal thickening or on a fibroatheroma. Thrombosis is present and might or might not be occlusive. No communication of the thrombus with the necrotic core
	Calcified nodule	Eruptive (shedding) of calcified nodule with an underlying fibrocalcific plaque with minimal or no necrosis. Thrombosis is usually not occlusive
Healed lesions	Healed plaque rupture, erosion, or calcified nodule	Healed lesion composed of smooth muscle cells, proteoglycans, and collagen type III with or without underlying disrupted fibrous cap, necrotic core, or nodular calcification. Lesions can contain large areas of calcification with few inflammatory cells and have a small or no necrotic core. The fibrotic or fibrocalcific collagen-rich plaque is associated with significant luminal stenosis. Absence of thrombosis

An updated version of the modified AHA classification published in 2016, which was based on the original AHA classification published in the mid-1990s

plaque on the cerebral artery has not yet been brought up, but its nature is not thought to be different from the actual nature of atherosclerosis, although the organ and the diameter of the artery are slightly different. Thus, it is appropriate to understand ischemic stroke due to large-artery atherosclerosis based on this [6]. As mentioned in this classification system, atherosclerotic plaque associated with thrombosis can be in the form of plaque rupture, plaque erosion, and calcified nodule. How these three lesions cause thrombosis will be discussed below.

1.3.1.2 Plaque Rupture

Plaque rupture consists of a necrotized core portion and a ruptured fibrous cover on the portion, and the cover is generally infiltrated by macrophage and T cells. The ECM of the fibrous cover consists of type 1 collagen, and VSMC is found extremely rarely. The thrombus

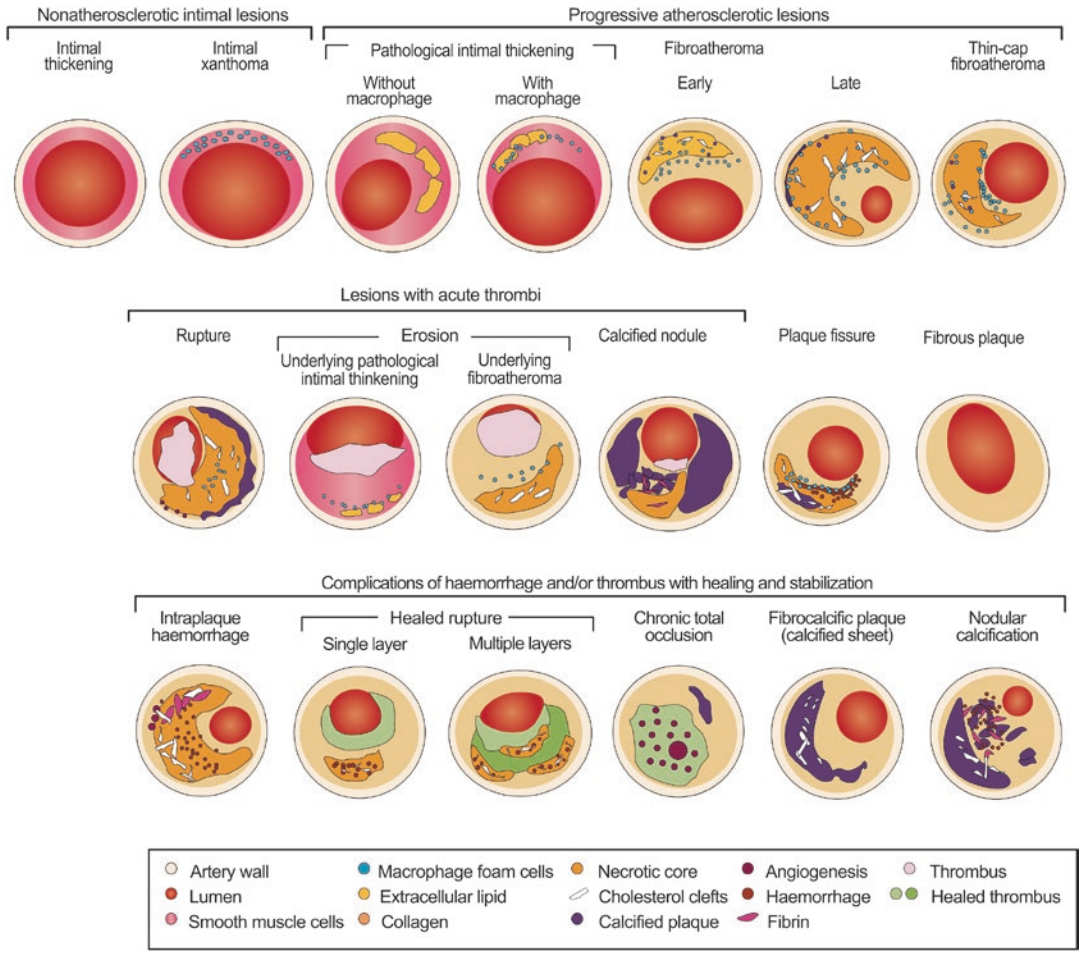

Fig. 1.6 Schematic figures showing composition and morphology of atherosclerotic lesion according to the classification suggested by the American Heart Association

found in the ruptured portion is mostly composed of platelets (white thrombus) and changes into a red thrombus with the image that the red blood cells are embedded in the fibrin layer (lines of Zahn) in the distal or proximal area rather than in the embedded area. If the fibrous cover is ruptured at rest, the rupture occurs in the shoulder area that is considered the weakest in the plaque, and if it occurs when the patient is exercising, rupture is known to occur with the same frequency in the shoulder and center areas. It is applied to the coronary artery, however, and the ruptured site of the plaque in the cerebral artery is not well known. With regard to the underlying mechanisms, there is a possibility that shear stress and tension, which affect the protease secretion from the macrophage and plaque, influence the rupture of plaque. Additionally, for fibrous cover, it is possible for a dying macrophage or a microcalcification derived from VSMC (>5 μm) to induce the separation of the cover due to the pressure and to cause plaque rupture.

1.3.1.3 Plaque Erosion

Plaque erosion is an arteriosclerosis lesion that may cause a thrombus due to the stripped surface of the intima composed of VSMC and proteoglycan matrix without rupture. Most underlying histological findings showing plaque erosion include intimal thickening and early or late fibroatheroma. The inner wall in

most plaque erosion cases is clean compared to the ruptured plaque and shows less inflammation, and the plaque rupture shows a positive remodeling finding but negative remodeling in erosion. Usually, significant calcification is not observed in erosion, but microcalcification is observed at around the 40% region. If a thrombus occurs in erosion, tissues are observed usually as a structure that activated VSMC is embedded into the substrate in which proteoglycan consisting of collagen type III, hyaluronan, and versican is abundant. This is in contrast to the finding that the fibrous cover mainly consists of biglycan, collagen type I, decorin, etc. in ruptured or stable plaque. The lipid level in the patient's blood is irrelevant to the occurrence of plaque erosion, and association with smoking has been reported, but verification of such is required. It has been known that distal microembolism more frequently occurs in a thrombus caused by plaque erosion than in a thrombus caused by plaque rupture. Plaque rupture and plaque erosion were briefly shown in Fig. 1.7.

1.3.1.4 Calcified Nodule

The rarest type of arterial thrombosis is a calcified nodule. The calcified nodule is the rarest cause of thrombosis even in coronary artery disease, accounting for only 5% of the causes, and shows the highest frequency in the coronary artery, in which calcification is considerably advanced. The incidence of calcification of an atherosclerotic lesion is much lower in the cerebral artery than in the coronary artery, and as such, it is difficult to know the frequency of the occurrence of atherosclerotic lesion in ischemic stroke. In this lesion, the mechanism of thrombosis development is unclear. One hypothesis is that the calcified sheet is ruptured by the physical pressure, and if it is decomposed into small nodules, fibrin is accumulated around them, and as a result, the accumulated fibrin can erupt above the plaque. The presence of fibrin within a plaque is common in the non-erupted calcified nodule lesions, but it is in the state of non-linkage with the lumen and is likely to have been derived from the damaged surrounding capillaries. The projectile calcified nodule is common in the asymmetrical-shaped lesion, and due to such eruption, there is a possibility of promoting platelet activation. This lesion is more frequently observed in the elderly. The calcified nodule should not be confused with nodular calcification because nodular calcification may destroy the structure of media but adventitia involvement rarely occurs, and it is also independent from thrombosis.

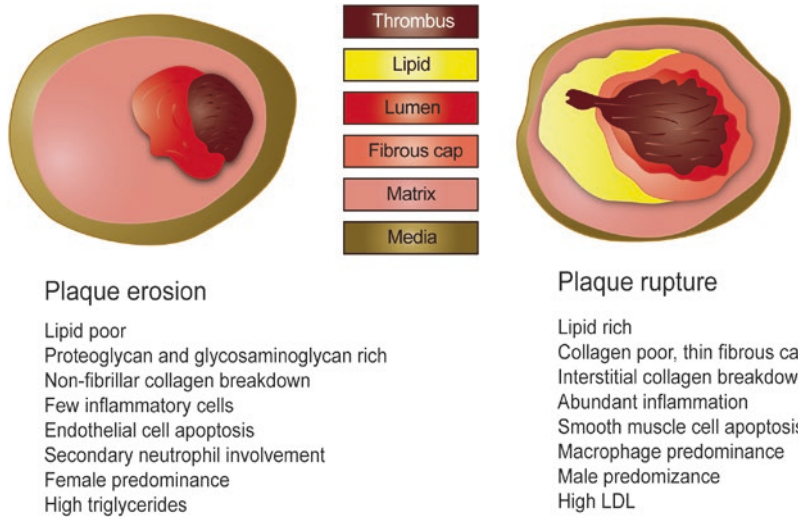

Fig. 1.7 Composition and characteristics of plaque erosion and plaque rupture

1.3.2 Mechanism of Occlusion in Small-Vessel Occlusion

It must be kept in mind that the mechanism of occlusion in small-vessel occlusion is quite different from that in large-artery atherosclerosis. Large-artery atherosclerosis is characterized by the existence of a white thrombus basically caused by platelet activation. The contribution of the platelet in small-vessel occlusion, however, is weak or unclear. In the identification of the occlusion mechanism in small-vessel occlusion, Miller Fisher's study played the greatest role. Dr. Fisher analyzed lacunar infarction in a serial section and confirmed that most lacunar infarction cases are caused by the occlusion of the penetrating artery, and that the diameter of most penetrating arteries is less than 225 μm. In such study, the proportion of lacunar infarction in a blood vessel with a more than 300-μm diameter was very small. It was assumed that the possibility of the occurrence of collateral circulation will be small in the case of occlusion that developed in the smaller vessels. In these vessels, occlusion occurs due to a mechanical blockage on the blood vessels by the degenerated vascular cells that form the wall of the blood vessels mostly denatured into lipohyalinosis. That is, it occurs when the denatured vessel wall itself suddenly blocks the blood flow, and infarction caused by a thrombus, as in large-artery atherosclerosis, very rarely occurs.

About 50% of the cases of occlusion caused by a thrombus in lacunar infarction occur in more than 300-μm-diameter blood vessels. The rest depend on the atherosclerotic plaque itself, or cases of the occurrence of microdetachment and of embolism are reported. Arteriolosclerosis that is a cause of thrombus is located in the proximal penetrating artery in many cases, and this pathological finding is called microatheroma. In particular, microatheroma occurring in the site branching from the great vessel is also called junctional atheroma, and in this case, the penetrating artery from which the thrombus that occurred here branches out is often completely closed.

In fact, the definition of lacunar infarction caused by small-vessel occlusion is ambiguous. Conventionally, it means cerebral infarction caused by the occlusion of the penetrating artery, but it is difficult to distinguish it without pathological findings in actual clinical settings because junctional atheroma that occurred in the large arteries at the previous step is also included in the range of lacunar infarction. Therefore, at the clinical settings in recent years, a less than 1.5- or 2-cm cerebral infarction that occurred deep inside as shown on the diffusion-weighted MRI is defined as lacunar infarction for classification. In this case, however, as even cerebral infarction with a hemodynamic cause or cerebral infarction caused by embolism meets this definition, misclassification is common. Therefore, the discussion of lacunar infarction caused by small-vessel occlusion should be based on a clear definition of it. In most cases, it would be most reasonable if lacunar infarction would be considered to be caused by mechanical occlusion due to the blood vessels denatured into lipohyalinosis.

1.3.3 Mechanism of Occlusion in Cardioembolism

Cardioembolism accounts for approximately 25% of all ischemic stroke cases. It can be generally thought that large-artery atherosclerosis, small-vessel occlusion, and cardioembolism account for 25% of all the cases, with very similar ratios. The remaining 25% of the cases include ischemic stroke with undetermined causes and that with rare causes. Cardioembolism develops when the patient has a heart disease causing blood stasis (e.g., acute myocardial infarction, left ventricular [LV] aneurysm, cardiomyopathy and myocardite, valve disease and/or prosthesis, and atrial fibrillation [AF]) [7]. As the blood directly going to the brain comes from the left side of the heart, the disease causing a thrombus at the left ventricle and left atrium can be seen as a cause of cardioembolism, except for diseases causing right-to-left shunt. The disease causing a thrombus at the left ventricle usually develops at the LV apex, and if the patient has LV aneurysm or acute myocardial infarction, the possibility of thrombus development at the left ventricle is high because myocardial infarction causes dyskinesia (akinesia or hypokinesia) in the heart wall at the left ventricle and consequently results in serious blood stasis. In

acute myocardial infarction, the trend of thrombus production is highest at the time of onset and decreases rapidly over time. If examined based on ischemic stroke, however, the proportion of ischemic stroke caused by old myocardial infarction is much higher than that of ischemic stroke caused by acute myocardial infarction. This is only because the prevalence of old myocardial infarction is much higher, and thus, the number is larger even though the possibility of thrombus formation is lower. Based on the same principle, the possibility of thrombus formation due to atrial fibrillation cannot be seen as very high, but its prevalence is very high in the elderly; thus, it is known as the highest cause of cardioembolism. Therefore, the mechanism of thrombus development by atrial fibrillation will be presented below.

1.3.3.1 Structural Consideration of the Left Atrium

The space attached to each atrium like a pocket is called an "appendage." The left atrial appendage (LAA) has a structure extending to the narrow entrance; thus, it is a probable site of blood stasis (Fig. 1.8). Therefore, LAA is a place where a thrombus most well develops at the atrium not only in a patient with atrial fibrillation but also in a patient with normal rhythm. As atrial fibrillation lasts longer, changes occur in the structure and tissue of the left atrium, and these changes are often associated with the frequency of thromboembolism. The change called "rough endocardium" refers to a finding showing a wrinkled appearance due to swelling, and is a status where fibrin and a thrombus can easily develop, with detached endothelial cells. Besides, findings of myocytic hypertrophy or necrosis, a mononuclear cell infiltrate, etc. are observed. The phenomenon where it is difficult to come back to the normal atrial rhythm even after successful cardioversion in atrial fibrillation patients can be explained by pathological findings like this. Additionally, due to these findings, atrial fibrillation patients are highly likely to require an anticoagulant despite the return to the normal rhythm.

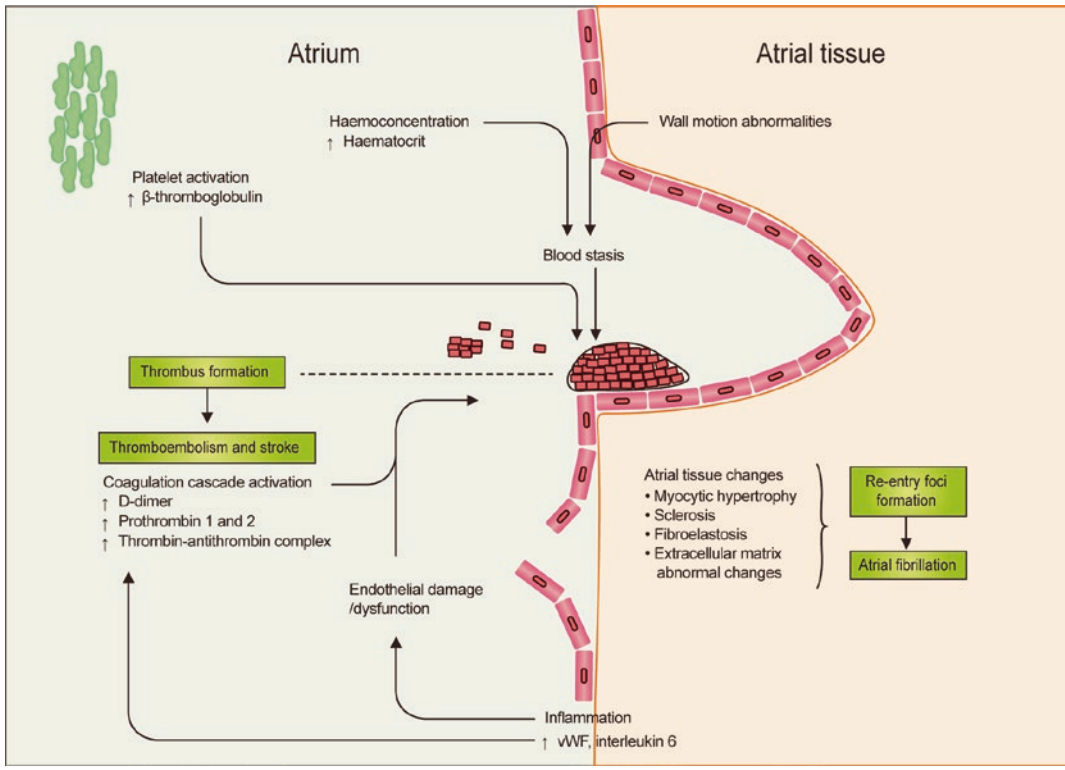

Fig. 1.8 Mechanism of thrombogenesis in left atrial appendage

1.3.3.2 Abnormal Blood Pooling in Atrial Fibrillation

In atrial fibrillation, blood stasis is worsened due to the progressive expansion of the left atrium as well as blood stasis or pooling due to atrial contraction failure [8]. This condition is further exacerbated if mitral stenosis occurs. The expansion of the left atrium increases thrombosis, namely, cerebral infarction, which can be confirmed in many studies in which the size of the left atrium was standardized, adjusting to the size of the body. The blood stasis in the left atrium or left atrial appendage is confirmed with spontaneous echo contrast (SEC) in transesophageal echocardiography (TEE), and SEC is known to be directly associated with the occurrence of stroke. SEC is known to last in about one-third of the cases after atrial fibrillation returns to the normal rhythm, which can explain why persistent anticoagulation therapy is required in this case.

1.3.3.3 Hypercoagulation Status of the Blood

It is known that the fibrin turnover increases in acute/chronic atrial fibrillation, but this actually does not seem to be directly associated with atrial fibrillation and with a structural problem of the heart. Nevertheless, there have been many reports that hypercoagulation biomarkers increased in atrial fibrillation in that ischemic stroke occurred compared to the normal rhythm. Taking into account the previous studies and making a reasonable judgment on the matter, it would be more reasonable to say that the incidence of ischemic stroke is higher in people with atrial fibrillation whose underlying coagulation status was accelerated, than to consider that atrial fibrillation itself accelerates the coagulation status. As a recent study reported that D-dimer was useful in predicting LAA thrombus, there is a possibility for D-dimer to become an important biomarker in atrial fibrillation patients.

1.4 Changes in Brain Tissues According to Cerebral Ischemia

The mechanism of cerebral blood flow (CBF) regulation is very complex and was designed to regulate various mechanisms and important structural components complexly and precisely. Here, the mechanism and its components for regulating the normal CBF will first be discussed, and then the changes that occur in the brain tissues when cerebral infarction occurs will be described.

1.4.1 Mechanism for Regulating the Normal Cerebral Blood Flow

1.4.1.1 Cerebral Blood Flow

The brain of adults is only about 1,350 g and accounts for about 2% of the brain's weight, but an approximately more than 55 mL/100 g/min CBF is normally required, and the amount is about 750 mL/min for the entire brain, which accounts for 20% of the total cardiac output. The brain's oxygen consumption is 3.5 mL/100 g/min even at rest and approximately 50 mL/min for the entire brain, which accounts for about 25% of the body's total oxygen consumption. The ability of the brain to store energy for itself is very small, and much of the glucose that it needs as an energy source must be supplied from outside. The adenosine triphosphate (ATP) obtained in the process of decomposing glucose into carbon dioxide and oxygen is used as an energy source. Therefore, as the brain is very sensitive even to a very short interruption in the blood flow, it is one of the major organs to which blood must be supplied first even when the blood flow to the other organs in the body is insufficient. In general, if the CBF is lowered to a level below 20 mL/100 g/min, electroencephalogram (EEG) and synaptic activity will be reduced, and if it is lowered to a level below 10 mL/100 g/min, irreversible neurological damage will occur.

1.4.1.2 Cerebral Autoregulation

If the brain is stable and if the level of carbon dioxide is properly maintained, the CBF will be very stably maintained [9]. Cerebral autoregulation refers to the operation mechanism for maintaining the CBF even though the atrial pressure from the heart changes. The autoregulation ability is normally maintained if the mean arterial pressure (MAP) is between 70 and 150 mmHg

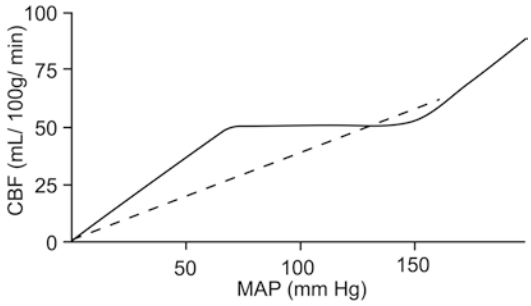

Fig. 1.9 Cerebral autoregulation (*MAP* mean arterial pressure, *CBF* cerebral blood flow)

(Fig. 1.9). The minimum mean arterial pressure in which autoregulation is possible is about 50 mmHg, but it is an available value only in some animals; for humans, a higher pressure is required. The cerebral perfusion pressure (CPP), defined as the value obtained after subtracting the intracranial pressure (ICP) from the mean arterial pressure (MAR) (CPP=MAP-ICP), is the most desirable tool for measuring the CBF, but it is almost impossible to obtain its value by actually measuring it at the clinical setting because there is no easy way to measure the ICP noninvasively. Usually, when the normal ICP at the standing position is considered to be about 10–15 mmHg, the minimum MAP for which autoregulation is possible is about 70 mmHg, and the lower limit of the minimum CPP is about 55–60 mmHg. If the CPP deviates from the range of autoregulation to the extent that it falls below the lower limit, the CBF passively depends on the blood pressure and consequently changes linearly according to the CPP. Even in a case where autoregulation operates within the normal atrial pressure range, a rapid change in the arterial pressure may cause a transient change in the CBF. If a person's CBF is rapidly reduced, the person usually faints (syncope).

The following is a step-by-step description of the change that occurs in the CBF depending on the change in the blood pressure (Fig. 1.10). If the blood pressure decreases, the CPP will also decrease, and as the arteries of the brain expand, the CBF will be relatively constantly maintained (stage 1). If the CPP is continuously reduced, however, it eventually goes beyond the limit of autoregulation ability, and the CBF will gradually decrease. In this stage, the CBF is reduced, but due to the increase in the oxygen extraction fraction, more oxygen will be extracted, and the cerebral metabolic rate will be relatively constantly maintained (stage 2). Here, if the blood pressure drops further, despite the increase in the oxygen extraction fraction, the brain metabolism will be lowered, and cerebral ischemia will occur (stage 3).

Cerebral perfusion pressure (CPP) is defined as the difference between the pressure of the blood flow to the brain and the venous back pressure. The venous back pressure is in the very low level unless the intracranial pressure significantly rises or the flow of the vein is not blocked, and as a result, the CPP can be seen to have a similar change with the mean atrial pressure. As the CBF is determined by the CPP and the cerebrovascular resistance (CVR), it is expressed by the formula CBF=CPP/CVR. If the CPP is constant, the local or partial change in the blood flow will depend on the change in the CVR, and the CVR will be determined complexly by the physical factors, including the blood viscosity and the length and diameter of the blood vessel, and by the biochemical factors, such as the arterial pressure of carbon dioxide ($PaCO_2$).

1.4.2 Structural Factors Involved in the Regulation of the Cerebral Blood Flow

1.4.2.1 Regulation by the Nervous System and the Neurovascular Unit

First, the nerves around the blood vessels play a very important role in the blood flow. Since recently, the theory that the vascular endothelial cells, the nerves around the blood vessels, and the astrocytes play a role in the blood flow as one functional unit rather than as separate units has gradually been admitted as a dogma. The functional unit is called "neurovascular unit" (Fig. 1.11) [10]. The nerve cells acting on the neurovascular unit can be divided into extrinsic and intrinsic innervation. Extrinsic innervation refers to vessel control by the nerves derived from outside. It is divided into the nerves derived from three nerve ganglions (the trigeminal, superior

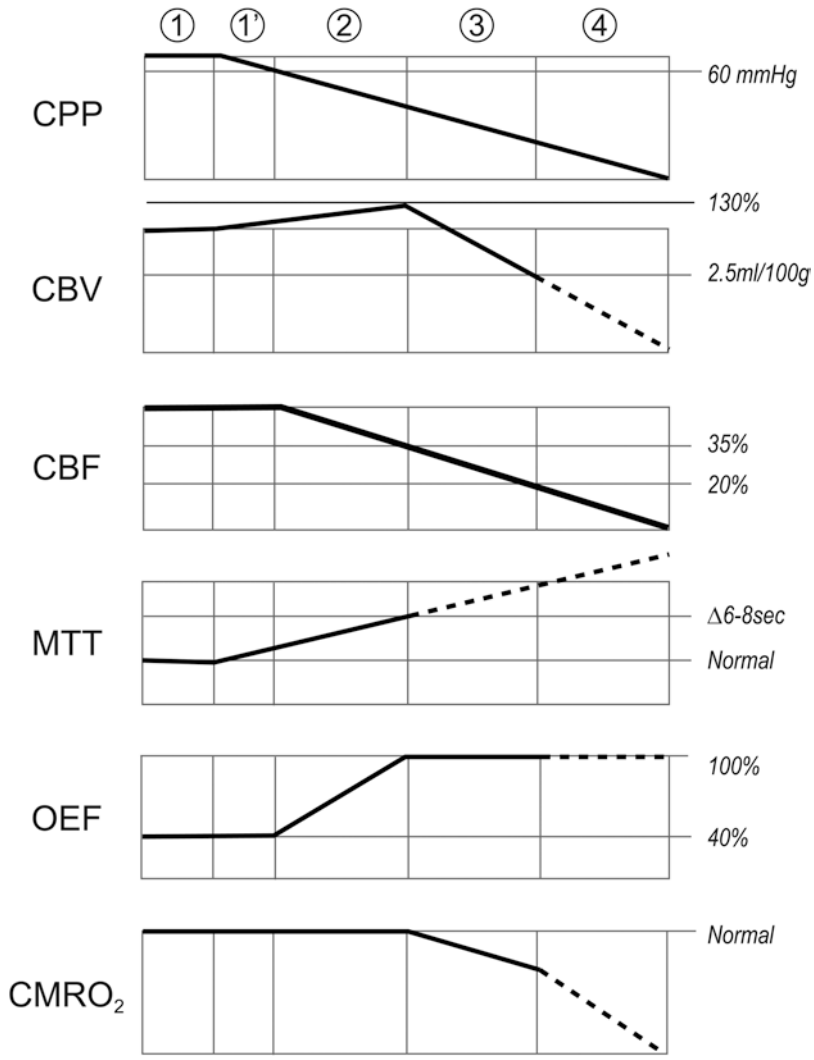

Fig. 1.10 Changes of cerebral blood parameters according to changes of CPP (*CPP* cerebral perfusion pressure, *CBV* cerebral blood volume, *CBF* cerebral blood flow, *MTT* mean transit time, *OEF* oxygen extraction fraction, *CMRO2* cerebral metabolic rate for oxygen)

cervical, and sphenopalatine ganglions), which are the pathways of the sensory, sympathetic, and parasympathetic nerves, respectively. If the blood vessel leaves the Virchow-Robin space and enters the brain parenchyma, the extrinsic innervation is discontinued, and intrinsic innervation begins. Intrinsic innervation is achieved by the subcortical interneuron derived from the distal area or the local interneuron and is achieved through connection to the astrocyte foot process rather than directly being attached to the blood vessel.

1.4.2.2 Vascular Endothelial Cell

The vascular endothelial cells play a central role in the CBF regulation. To date, four substances regulating the function of the endothelial cells have been well known: nitric oxide (NO), endothelium-derived hyperpolarization factor (EDHF), eicosanoids, and endothelins.

NO is a diffusible substance that activates guanylate cyclase and is present in the smooth muscle cell and is considered a substance that has the strongest impact on vascular enlargement. Guanylate cyclase activated by NO relaxes the

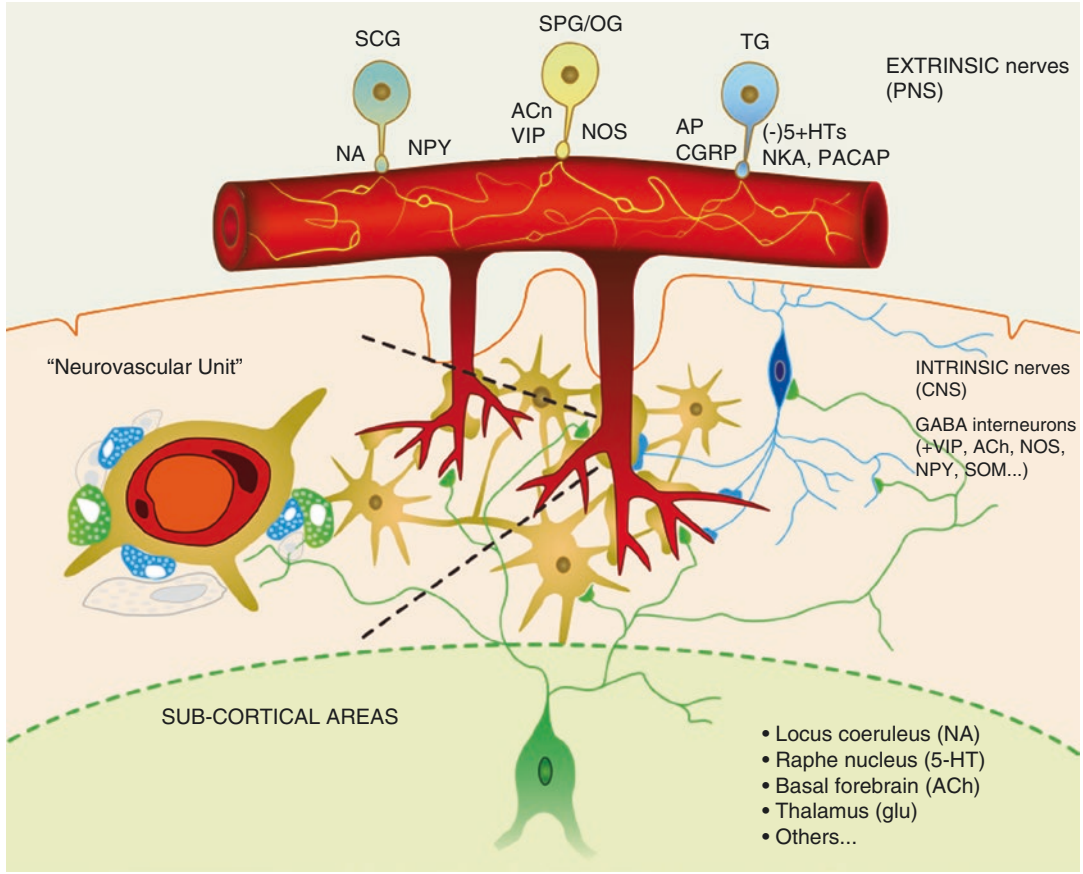

Fig. 1.11 A schematic figure of a neurovascular unit

smooth muscle through the blockage of the voltage-gated calcium channel or the protein kinase G (PKG) activation of the K+ channel while synthesizing cGMP. The enzyme synthesizing NO has several isoforms, and endothelial NOS (eNOS), existing in the cerebral blood vessel, especially in the vascular endothelial cell, plays an important role. EDHF is another diffusible molecule that is activated by the hyperpolarization of the vascular smooth muscle cell and is suppressed by the K+-channel blocker. Eicosanoids are a series of vasoactive substances derived from arachidonic acid, and the following three enzyme systems have been confirmed: cyclooxygenase (COX), lipoxygenase (LOX), and epoxygenase (EPOX). These three enzyme systems are not limited to the endothelial cells but are activated in various cells, including the platelets. Also, as a certain component activated by the enzymes is involved in vascular enlargement, and as another component is involved in vascular contraction, the effect on the overall CBF is determined depending on the activation ratio and locations of these enzymes. Another substance that affects the CBF is endothelin. The system consists of two receptors (ET_A and ET_B) and three ligands (ET-1, ET-2, and ET-3), and its effect on the blood vessels seems to be determined by the receptors rather than the ligands. The ET_A receptor mainly exists in the vascular smooth muscle cells, is stimulated by ET-1 and ET-2, and mediates vascular contraction. On the other hand, the ET_B receptor mainly exists in the vascular endothelial cells, is stimulated by all the three aforementioned ligands, and mediates vascular enlargement. Endothelin is a system associated with a continuous effect rather than with the immediate regulation of the CBF. It is highly

likely to play an important role in pathological conditions such as cerebral ischemia rather than in the regulation of the CBF at rest.

1.4.2.3 Astrocyte

Astrocyte plays a very unique role in CBF regulation. The projection extending from the astrocyte to the outside periphery wraps the capillaries and physically contacts the microvascular structure. Astrocyte has been thought to basically function as the warehouse of extracellular K+, and the possibility of mediating the nerve-blood vessel interaction through communication between the cells through the gap junction was recently raised. As astrocyte has a glutamic acid receptor increasing the level of intracellular calcium, the foot process of astrocyte is assumed to recognize the synaptic signal and to mediate the expansion of the blood vessel associated with it.

1.4.3 Change in the Brain Tissue Caused by Ischemic Stroke

Ever since Astrup first suggested the concept of ischemic penumbra, it has been understood in different ways. The penumbral region is the area typically confirmed around the ischemic core in which the blood flow is reduced to the extent that the ion channel can be maintained even though the electrical activity of the nerve cells cannot be maintained despite the fact that necrosis is not reached. As the electrical activity cannot be maintained, neurological defects occur due to this part, but in this part, if the blood flow is reopened, the previous activity will be regained, and consequently, the patient's symptom will be alleviated. If the decreased blood flow continues, however, various signals (excitotoxicity, spreading depression, oxidative stress, inflammatory response, etc.) exacerbating the brain metabolism function will be generated from the core of the cerebral ischemia to the periphery, and eventually, the patient's symptoms will be exacerbated due to the expansion of the ischemic core [11]. Therefore, properly defining the penumbral region currently confirmed in cerebral ischemia, which is an ultimate goal, is the starting point of ischemic stroke treatment. As it is not easy, however, to clinically visualize the penumbral region for treatment, attempts have been made to approach such region in various ways. Here, several influential concepts will be introduced.

1.4.3.1 Confirmation of the Penumbra Region Through Diagnostic Imaging

In clinical settings, the most appropriate way to define the penumbral region of cerebral infarction is to use neuroimaging. A method of confirming the penumbral region using several protocols has been known while performing MRI for ischemic stroke patients at the early stage. Perfusion-weighted imaging (PWI) can sensitively check the site in which the CBF is reduced, and the site is defined as the cerebral ischemia site, where the blood flow is reduced by vascular occlusion. After diffusion-weighted imaging (DWI) defines the infarction core that has been very severely damaged by vessel occlusion, the rest of the parts, excluding the DWI lesions from the PWI lesions, are collectively defined as the penumbral region (diffusion-perfusion mismatch) (Fig. 1.12) [12]. Here, the DWI high-density part is considered the core of cerebral infarction, but actually, looking at the estimate of

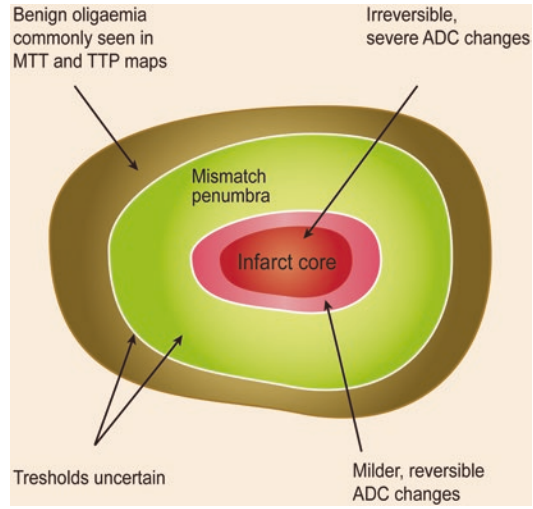

Fig. 1.12 A conceptual figure of diffusion-perfusion mismatch (*MTT* mean transit time, *TTP* time to peak, *ADC* apparent diffusion coefficient)

the apparent diffusion coefficient, a high density is observed before the energy metabolism is completely depleted. Therefore, the DWI high-density part can be said to be seen as larger than the core of the actual cerebral infarction. Also, as PWI is used only when there is a problem with the appropriate oxygen supply, it cannot be thought that PWI shows the ischemic site perfectly. In conclusion, it is reasonable to consider the diffusion-perfusion mismatch site as the sum of the outer portion of the penumbra and the normal tissue part. For this reason, efforts have been exerted to find the penumbra through another method. One of such methods is clinical-diffusion mismatch. In this method, the outline of the ischemic area is estimated by neurological symptoms and signs and compared with the DWI lesion part confirmed at the time. It is a method that is considerably reasonable clinically but has limitations in that standardization is not easy therein, and different opinions can be derived depending on the knowledge or skills of the physician. PET (positron emission tomography) is the golden standard that can confirm the penumbra based on its original definition, but it is impossible to actually utilize it because it is expensive and is impossible to use in emergency situations.

1.4.3.2 Penumbra Region Defined with Biochemical Indicators

To overcome the limitation of the penumbra region confirmed by the imaging indicators described above, the use of biochemical indicators have been suggested. This is an application of the fact that the various molecular biological mechanisms associated with cell death become more active as they move to the core from the penumbra region. If the CBF is reduced, the ATP will decrease, and if the Na+/K+ pump does not work, the extracellular glutamic acid level will increase. These will increase the intracellular calcium level by stimulating the glutamic acid-related receptors (N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). This mechanism is called "excitotoxicity." The intracellular calcium increased through this will increase the generation of free radicals and will ultimately synthesize toxic peroxynitrite radicals by activating neuronal nitric oxide synthase (nNOS). That is, the most important mechanism that cell death due to cerebral ischemia spreads is the diffusion of the extracellular glutamic acid from the cerebral infarction core to the periphery (Fig. 1.13). Glutamic acid is also a key mediator of peri-infarct depolarization and spreading depression. It causes acidosis due to the destruction of the ion homeostasis, increases the energy requirement, and causes the excessive release of neurotransmitters. In animal experiments, brain imaging (e.g., chemical shift imaging) has been attempted to confirm the increase of such glutamic acid. The mechanisms accelerating cell death in the penumbra along with excitotoxicity due to glutamic acid include oxidative stress, nitric oxide overproduction, release of inflammatory cytokines (e.g., tumor necrosis factor-α and interleukin-6), expression of adhesion molecules (e.g., intercellular molecule adhesion-1, vascular cellular adhesion molecule), and production of matrix metalloproteinases.

Contrary to the expectations, active protein production in the penumbra can play the role of an indicator. In general, if cell death starts, protein production and cell metabolism will rapidly decrease, but the stress protein, such as heat shock protein 70 (HSP 70), will be greatly amplified. HSP 70 is a type of intracellular chaperone that handles ordinary intracellular mechanism damage, and when certain cells are extremely stressed, it rapidly increases to suppress cell death. The site where HSP 70 is amplified is sometimes defined as the penumbra (Fig. 1.14). Apoptosis is also a characteristic of the penumbra. If certain cells are rapidly damaged, as mentioned above, they will proceed to the process of necrosis through excitotoxicity, but when moderate damage occurs, as in the penumbra, programmed cell death will be shown, in which the cells will commit suicide according to the planned intracellular mechanism. This is called "apoptosis." Apoptosis is a type of cell death through a planned mechanism; thus, it is characterized by the expression of very distinctive substances. The typical mechanisms include isolation of cytochrome c from the mitochondria and activation of caspase protein. If molecular imaging is

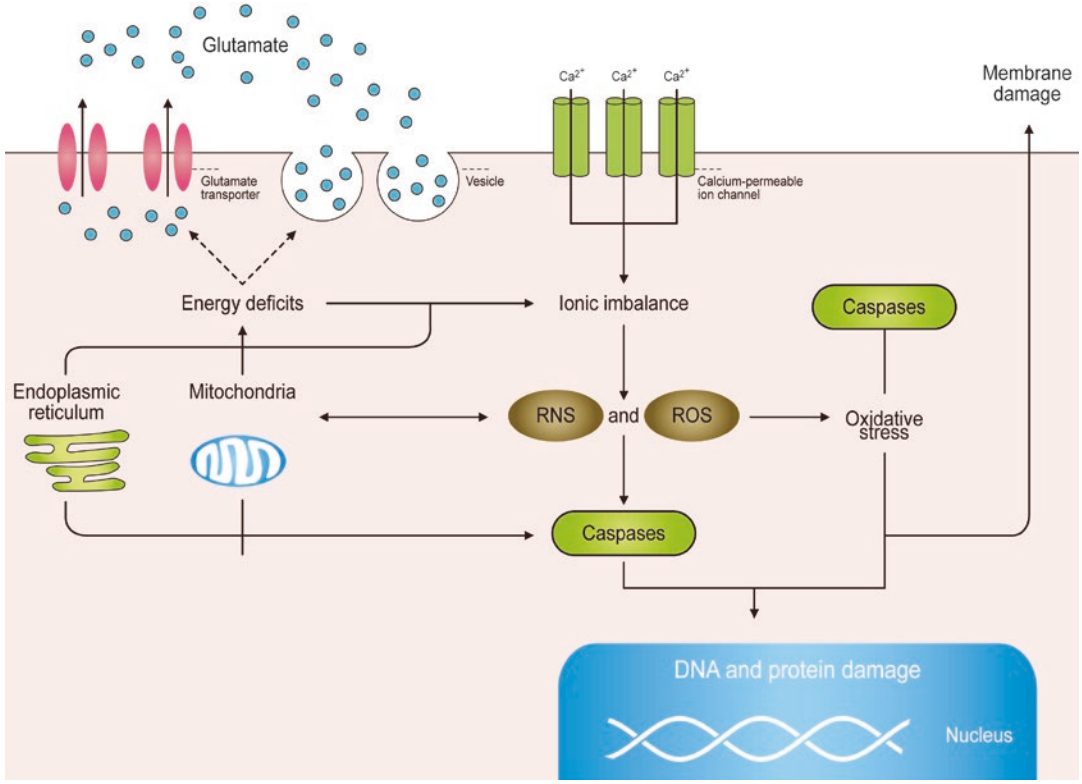

Fig. 1.13 A cell death pathway caused by cerebral ischemia

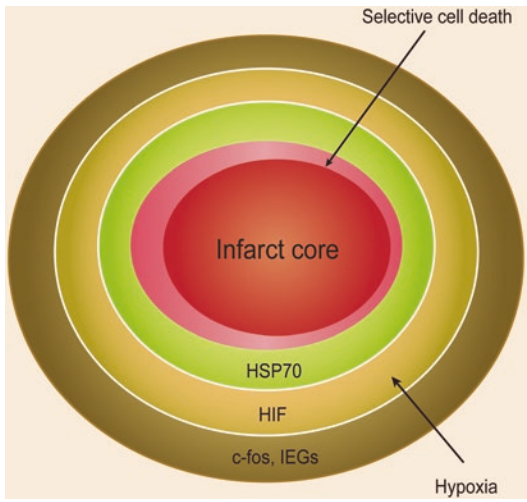

Fig. 1.14 A conceptual figure of penumbra defined by biochemical indicators (HSP70, heat shock protein 70; HIF, hypoxia-inducible factor; IEG, immediate early gene)

possible as a test with high sensitivity and specificity, it can define the molecular biological penumbra. The molecular biological penumbra becomes the target site for examining the effect of neuroprotection drugs on ischemic stroke.

1.4.3.3 Penumbra Region Defined by the Regeneration Mechanism of the Brain

Various molecular biological mechanisms activated by cerebral ischemia often have two sides. These aggravate the secondary brain injury by worsening the inflammation of the brain at the early stage, but after they are stabilized, they repair the brain injury and even play the role of promoting regeneration. In particular, proteins, cytokines, or cells related to inflammation, and typically monocytes, especially macrophages, play such a role. The

macrophage that worsens inflammation at the early stage is called M1 macrophage, and the cell that repairs the damage later is called M2 macrophage as mentioned earlier. The roles of these inflammation cells are not actually significantly different from that in the case of infectious inflammation, but as they are irrelevant to the invasion of microorganisms by foreign substances, the inflammation that they are associated with is called "sterile inflammation." Like this, there is an opinion that the site associated with recovery of brain injury must be newly defined as the penumbra.

Conclusion

In this chapter, the pathophysiology of ischemic stroke was very extensively and deeply discussed. Ischemic stroke developing in the brain is a disease with very diverse subtypes, unlike acute myocardial infarction. In fact, as the onset mechanisms of these subtypes according to the TOAST classification system are too different, it is appropriate to see ischemic stroke as a cerebral infarction syndrome actually caused by a totally different mechanism. The blood vessel occlusion mechanisms are all different in small-vessel occlusion, large-artery atherosclerosis, and cardioembolism. In large-artery atherosclerosis and cardioembolism, the blood vessel is occluded by a thrombus, but its appearance and onset mechanisms are also different. Therefore, the patient's initial treatment and prevention method must be determined taking into account the onset mechanism. The brain usually keeps the CBF constant through autoregulation, but if the local CBF decreases due to ischemic stroke, and the cerebral ischemia condition lasts, cerebral infarction will occur after all. In the areas surrounding the cerebral infarction site, a penumbra region that has not yet reached complete infarction exists, which becomes a treatment target that should be recovered into normal tissues in early acute-phase treatment. It must be kept in mind that the understanding of the pathophysiology of ischemic stroke is the foundation of understanding the various clinical and basic aspects of stroke.

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