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REVIEW ARTICLE

Primo Vascular System as a New Morphofunctional Integrated System

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Abstract
The purpose of this review is to describe the methodology, instruments, and subject animals used until now for studies of the meridian (Kyungrak) system and the primo vascular system (PVS). The PVS is observed as an anatomical system distributed in cavities, organs, and tissues throughout the body. We analyzed the most important points of the PVS based on the results obtained until the present. Our main effort has been directed to describing the main thesis relating to the morphological structures and their topography, the functional mechanisms of the PVS, and possible roles of the PVS in pathological processes. The substance of the PVS in all its aspects is as a system covering the whole body and regulating and coordinating the biological processes that are the basis for life. In conclusion, we suggest that the finding of the PVS represents the discovery of a new integrated morphological-functional system.

1. Introduction

The morphological architectonics and functions of the primo vascular system (PVS) are the two aspects for which combinations thereof may drastically change our current understanding of basic biology and its related branches of medicine, veterinary medicine, and sciences such as morphology, physiology, biochemistry, biophysics, pathology, etc. When we investigate the new anatomical system, the first surprising finding is that morphological

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science had not discovered this system until now. The reason lies in the suspicion of Western medicine toward the acupunctural meridian system. The therapeutic effects of acupuncture have been accepted worldwide [1—3]. Western medicine, however, has refused to see the obvious possibilities of an anatomical substance whose existence could be the framework for acupuncture treatment, which has been used in traditional Eastern medicine for thousands of years. Modern science cannot explain the long-standing successful existence and functional paths of the curing modality for traditional Eastern medicine. Another reason is that current science is convinced of the correctness of the fundamental basis of biological science, but cannot explain many questions concerning the mechanisms of the processes of life. The new system was not being pursued in the right place, and it was not investigated with adequate methods in the past as it has been recently by scientists from China, Japan, and Russia [4]. It would appear that the PVS only comes to light when numerous appropriate methods are applied.

We can determine two periods for the discovery of the new morphological-functional system. The first one includes the five papers from Bong-Han Kim from 1962 to 1965 [5—9], and we have commented on them in a detailed manner in another article of this journal [10]. Bong-Han Kim revealed much, suggested more, but left many details unanswered. The second one, which we would call 'a rediscovery of the PVS,' is from 2002 until now, and it was made mainly by the scientists from Seoul National University (SNU), Korea. They developed the methods to detect and identify the new anatomical system [11,12]. In 2011, the SNU team was expanded to the Nano Primo Research Center headed by Prof. K. S. Soh with the main purpose of further investigation into the PVS. He named the new system the primo vascular system, and the Bonghan ducts and corpuscles for the channels and the nodes were renamed as primo vessels (PVs) and primo nodes (PNs), respectively. The SNU group has published about 56 articles and obtained more than 200 citations concerning this subject. (These data were obtained from the BioInfoBank Library, Warszawa, Poland.)

Today the substance of the PVS in all its aspects is suggested to be a system covering the whole body, and regulating and coordinating the biological processes that are the basis for life. In modern biological sciences, the unity of organisms and the environment and the regulation mechanisms involved in the coordination of all body systems constitute fundamental and still unsolved problems.

The purpose of this review is to describe present-day findings and to analyze the most important points of the PVS as a new discovery. In this paper we use the terminology adopted at the International Symposium on the Primo Vascular System held in 2010 [11].

2. Methodology, instruments, and subject animals

2.1. Bong-Han Kim's work on the meridian system

Bong-Han Kim's study of the meridian (Kyungrak) system can be divided into three parts [6]: a morphological study, an experimental physiological study, and a biochemical and histochemical study. His morphological study (the first part) on the Kyungrak system was done through anatomical observations on superficial and profound Bonghan (BH) corpuscles (primo nodes) in the living body. He found that the superficial BH corpuscles were distributed in the skin and that the profound BH corpuscles were positioned in the organism under deep skin. He made numerous descriptions of the corpuscles according to their locations, forms, and shapes. Many histological studies were performed with microscopes, and the microscopic images were presented in the ranges of tissue and cellular levels corresponding to magnifications of 100 ~ 500 times. The morphology of the BH ducts [primo vessels (PVs)] was also studied through anatomical observations and histological methods. One of the special characteristics of BH ducts is that they are composed of many subductules with endothelial cells with rod-shaped nuclei. That observation was made during a phase-contrast microscopic study.

Bong-Han Kim's findings on the corpuscle and duct system naturally induced further experimental physiological studies (the second part). The duct systems were distributed throughout the living body, and they ran along the outsides and the insides of blood and lymphatic vessels. This may be considered to be one of the distinctive features of the Kyungrak system. In his second study, he tried to elucidate the question of the circulation of the BH liquid that flows through the BH ducts. He used radioactive tracers to identify the circulation and adopted electrophysiological methods for research into the excitability and the conductivity of the Kyungrak system. He also invented a dye injection method. However, the methods of dying being kept secret and incomplete descriptions of the scientific protocols were the main reasons for his findings being forgotten for many years. The following relates to the methods and protocols used in the past and the current modern methods. In his reports [5—9], Bong-Han Kim makes references to a series of methods, such as anatomical, histological (Hematoxylin and Eosin (H&E), Mason's trichrome, Verhoff, silver staining, feulgen reaction, Acridine orange), dosimetry of radioactivity, radio-autographical, histochemical, and a "mysterious" blue staining, but without describing any details of the scientific protocols. He mentioned the use of the "mysterious" dye many times without giving any detailed information on the procedure for using it. He used different types of microscopes, such as stereomicroscopes, as well as phase-contrast, inverted, luminescent, and transmission electron microscopes.

The third part of his studies focused on the biochemical and histochemical analyses of the corpuscle and duct system. Various forms of the phosphorus contents in the BH ducts were determined by using the Fiske-Subbarow method and the Schmidt-Thannhauser extraction procedure. Granules in the BH corpuscles and ducts showed positive reactions with the Unna-Pappenheim method, as well as positive Feulgen reactions. As a result of his experiments, he noticed that the BH corpuscles and ducts contained more nucleic acids, especially DNA, than any other tissues. Based on his observations, he concluded that the functions of the Kyungrak system were closely related to nucleic acids and to DNA in particular.

Bong-Han Kim's claims could not be reproduced because the formula for the staining dye was undisclosed. In 1966, Kellner [13] used histological methods to deny Kim's claims. It is difficult for us to be satisfied with the extremeness of Kellner's position, for rejecting Bong-Han Kim's whole theory, which was created by using the many methods, described above with only routine histological methods used by Kellner is not possible. Only Fujiwara and Yu [14] were able to partially confirm Bong-Han Kim's findings.

2.2. SNU group's work on the primo vascular system

In 2002, Prof. K. S. Soh started an intensive re-investigation into Bong-Han theory by using modernized techniques such as fluorescent microscopy, confocal microscopy, and electron microscopy. The Progression of the rediscovery of the PVS was determined by the development of methodology and by the team's creativity. The first key technique developed by the SNU team was the intravenous injection of a 10% dextrose solution to replace blood with a transparent liquid for observation with a stereomicroscope [15—17], but with low success rates because the PVS could not be clearly distinguished from fibrin strings (Fig. 1) [12].

In 2008, there was a major step in the methodology. The SNU group discovered the Trypan blue technique for the specific visualization of the PVS [18]. This technique is simple, but very effective. The same group had previously obtained successful results by using Janus Green B (Fig. 2) [19] and Alcian blue [20,21]. In fact, the SNU group has applied all the standard methods used by Bong-Han Kim, as well as several new ones [22].

During the last decade, a series of conventional and modern methods and technologies have been utilized. Confocal laser scanning microscopy [23]; various types of electron microscopy, such as scanning electron microscopy (SEM), cryo-SEM, focused-ion-beam SEM, and high voltage transmission electron microscopy (TEM) [24—26]; X-ray microtomography [27]; atomic force microscopy [28]; fluorescent nanoparticle [29—33]; immunohistochemistry [34,35]; proteomic analysis [36]; the ELISA technique for hormone analysis [37,38],; and electrophysiological methods [39] have been employed [12]. Magnetic resonance image (MRI) and computed tomography (CT) have been tried, but no important results have yet been obtained [22].

Bong-Han Kim used primarily rabbits as laboratory animals. No data on other animals, including human subjects, were presented, but he mentioned that the PVS had been observed in various mammalian species, including humans, avians, amphibians, fish and invertebrates such as hydra, without suggesting any specific animal species [7]. The SNU team performed their investigations with laboratory animals such as mice, rats and rabbits. A few case studies have been reported for cows [40], pigs [41], and dogs [42]. As we mentioned in the other review [10], as the animals are divided from lower to higher, the PVS of animals can be divided in a similar way. The development of the PVS may be progressive, with the most developed one being in humans.

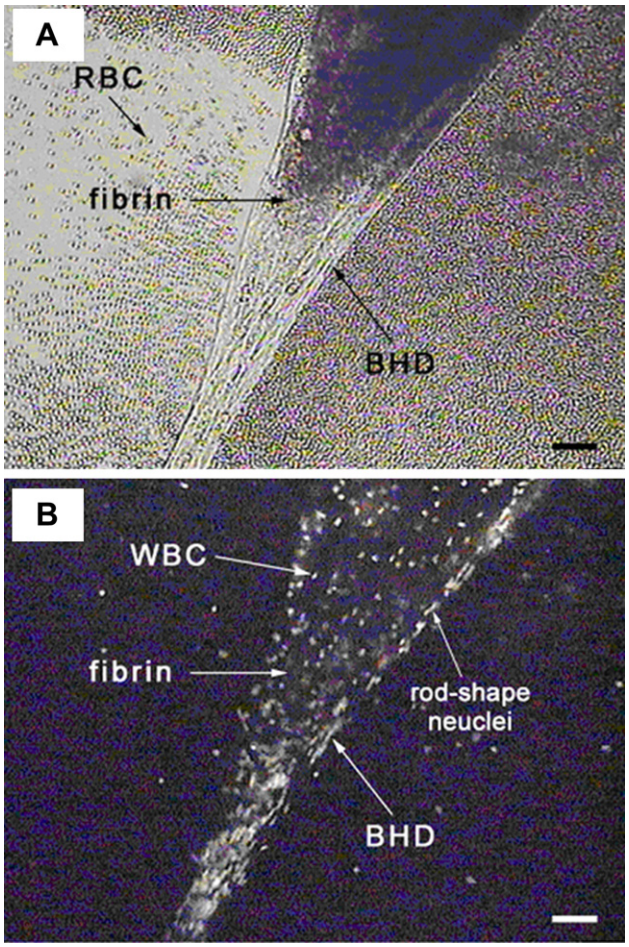

Figure 1 (A) Threadlike structure with fibrin observed by differential interference contrast microsope. Scale bar 50 μm; (B) acridine orange stained image of the same sample. Long rod-shaped nuclei can be seen from the threadlike structure [12, *J Acupunct Meridian Stud*. 2009;2:93—106]. Scale bar 50 μm.

3. Morphological characteristics of the PVS: actual anatomical systems, cavities, organs, and tissues

In this section, we describe Bong-Han Kim's findings, that have been confirmed, as well as the new anatomical structures that have been shown to include the PVS. Lee *et al*. [43] described PVs as freely floating in bovine heart chambers. This is the first report of the PVS in large animal organs. The authors did not say, but for the first time an organ obtained from an animal slaughterhouse was used for a PVS investigation. Use of organs after slaughter allows new approaches. First, it presents an opportunity for using large animals. Second, animals can be used some hours after they have died. Third, the PVS can be visualized after bleeding has occurred.

The PVS was observed in the caudal vena cava, the hepatic vein, the hepatic portal vein, the femoral vein, the aorta [15] and large lymph vessels along the caudal vena cava [19,27,29,30,44]. The PVs are located inside the vessels, as well as along the blood and the lymphatic vessel walls. The PVs inside the lymph vessels are close to the lymph valves

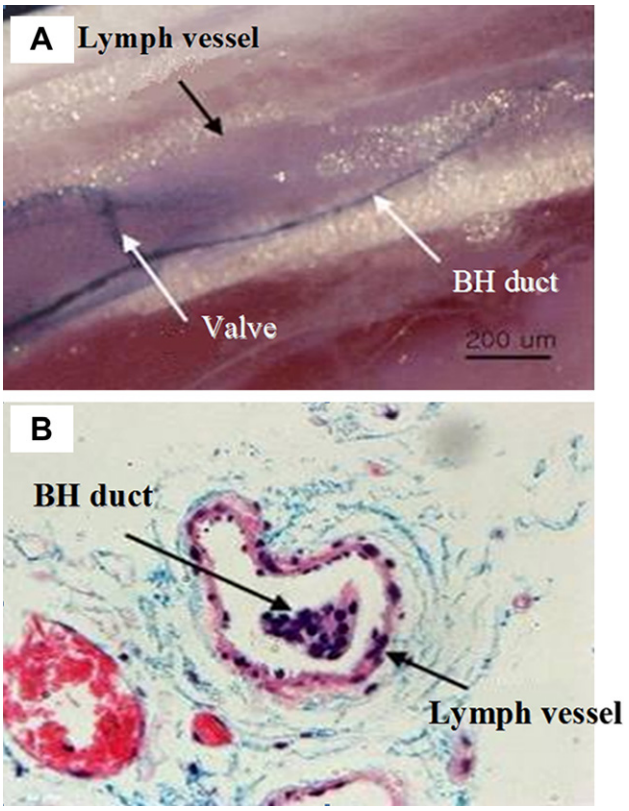

Figure 2 BHD (Primo vessel) inside a rabbit lymphatic vessel stained with Janus Green B [12, *J Acupunct Meridian Stud*. 2009;2:93—106]. (A) Stereo-microscopic view; (B) cross-section image of H&E stained sample.

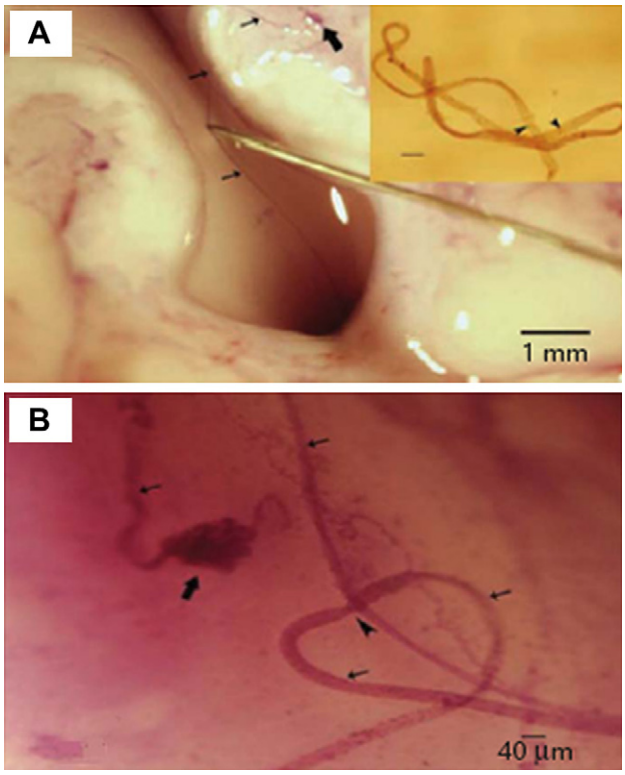

Figure 3 PVS found in the brain [12, *J Acupunct Meridian Stud*. 2009; 2(2): 93-106]. (A) Stereomicroscopic image of PVS in an aqueduct and third ventricle of rabbit brain. (B) Stereomicroscopic image of PV node and vessel taken from the brain.

[27,29], freely float in the lymph, and pass through the lymph valves. For better observation of the PVs inside the lymph vessels, pressing the sample between two glass plates gives an opportunity to temporally fix the PVs in the center of the lumen. It should be noted that the PVs [10] prepared in this way show good mechanical stability and that the fluid flow in the PVs cannot be stopped by the plate's pressure.

As shown in Fig. 3, the PVs and the PNs were found in the third ventricle, the fourth ventricle, and the cerebral aqueduct, along the central canal of the spinal cord [45], and on the arachnoid mater, cerebellum [46] and the perineurium and the epineurium of the sciatic nerve [46,47]. The PVs and the PNs were observed on the surfaces of visceral organs (liver, stomach, small and large intestines, bladder, spleen, kidney and omentum), the abdominal cavity [18,23—26], the hypodermal layer of the skin, the superficial fascia [21], fat tissue [48] and cancer fascia [49]. However, very rarely were the PVs observed to enter internal organ tissues [50].

Bong-Han Kim and K. S. Soh both proposed a classification of the PVS based on six subnetworks: superficial, intravascular, extravascular, organ surface, intraorgan, and neural [12]. The data show that the PVS exists in three morphological places. We propose to develop this classification of the topographical locations of the PVS. The first PVS morphological location is the PVS in internal cavities and lumens. Some PVs freely floating internal cavities (brain cavities and heart chambers) and in lumens (blood and lymphatic vessel's lumens, cerebral aqueduct, and spinal cord channel). The second PVS morphological location is the PVS within organ-covering membranes. The PVS appears within organ-covering membranes (serous membranes: parietal and visceral peritoneum which cover the abdominal wall and all internal organs; the pia mater and the arachnoidea of the brain). The third PVS morphological location is the PVS in connective and fat tissues (hypodermal layer, superficial fascia, epineurium and perineurium, vessel's adventitia, fat tissue and cancer fascia). We also propose a new classification of the topographical position of the PVS structures to replace Bong-Han Kim's description [6]. We propose to rename the superficial PVs and PNs as "receiving PVS." The interior-exterior PNs may be given the name "communicating PVS." This classification could be developed with "organic" and "extra-organic" parts of the PVS. We propose to rename the PVs and the PNs in the organs and on the organs as the "organic PVS." We propose to rename the PVs and the PNs that are between the organic and the receiving parts of the PVS as the "extra-organic" parts of the PVS.

There are no data whether the PVS exists in anatomical structures such as the head's organs (tongue, salivary glands, nasal cavity organs, and sensory organs as eyes, ears, ethmoidal labyrinth, vomeronasal organ), the neck's organs (esophagus and trachea), the thoracic cavity organs (lungs, esophagus, trachea, and pericardium), the pelvic cavity's organs (female generative system, urethra, accessory glands and male penis), the glands, the

autonomic nervous system, the muscles, and the bones. Further study is necessary to identify the connection of the PVS to these kinds of organs.

4. Functional aspects of the PVS

The PVs are surrounded by a membrane. The membrane consists of a high concentration of hyaluronic acid [27]. Hyaluron is responsible for cell growth and differentiation. Probably, the hyaluron could be involved with repairs of damaged PVs. The PVs consist of several sub-channels. The subchannels have double coats [10] and a layer of endothelial cells. Rod-shaped endothelial nuclei (10–20 μm) are hallmarks of the PVS [51–53]. The cells of the PVS show a smooth muscle-like excitability. The excitable cells have Ca-ion channels, which are necessary for cell movement [39]. The sub-vessels have adventitia containing connective tissue and an amorphous substance [6] as supporting tissue. Also the PVS often lies in connective tissue. Collagen is the main component of connective tissue. Collagen is an abundant molecule with special properties, and data indicate that it has properties of interference with photon emission emanating from biomolecular sources. This property of collagen to interfere with photon-emitting processes facilitates the possibility of tuning photon emission throughout an organism, and it is a step towards the hypothesis that metabolism is regulated by a photon field [54]. This supports Soh's hypothesis [55] regarding the PVS as an optical channel of biophoton emission. Biophotons may be the electromagnetic signals that play a key role in the processes of cell development and differentiation. DNA may act as a photon store and coherent radiator [55]. There is a suggestion that spontaneous ultraweak photon emission from cultured cells is mainly involved in the changes in the ploidy number that occur during the proliferative process of cancer cell lines [56]. This hypothetical light propagation function of the PVS may explain the instantaneous effect that often occurs throughout the entire body with the application of needles at acupoints [12,55].

The presence of chromaffin cells at acupoints [37,38] has provided a new view of their function as an endocrine catecholamine organ [12] besides the currently known adrenal medulla, postganglionic fibers, and Merkel cells [57]. Fujiwara proposed that the PVS is a hormone path that is more efficient than conventional blood flow paths.

The primo subvessels and primo nodes carry a liquid. The liquid was found to be rich in basophilic granules, which have been observed as individual granules and have been seen in groups of two or three, and as granular clusters [58]. There are different proteins [36], stem cell niches [48] or microcells [28,59,60] with much harder membranes than similar-sized apoptotic bodies [61], and hormones [37,38,62] in the primo liquid. The flow speed of the liquid was measured at 0.3 mm/s by injecting an Alcian blue solution into the PVS on the surface of the liver [63] and in range of 100–800 um/second when directly measured by using radioactive tracers [25,64,65], which values are significantly higher than those observed in lymphatic vessels [58]. This supports the concept that there are many morphological features that allow faster flow of the primo fluid [10].

Five types of cells float in the primo liquid [66]. Type four and five cells contain granules with DNA that do not exist in other body liquids. Type three cells are in the mitosis stage as the cells described by Bong-Han Kim [6]. The authors suggest that the PVS may be a channel for cell migration and that the fifth cell type is the first step of cell proliferation. The organ-surface PVs and PNs contain a significant number of monocytes, eosinophils, mast cells, and macrophages [24,26,67], supporting an immune function for the PVS (Fig. 4) [12].

The PVS in the vitelline membrane in eggs was observed within 16–24 hours of incubation, and the putative PVS was clearly developed earlier than the formation of the extra-embryonic vessels, let alone the establishment of the heart and intramembranous vessels [68]. This supports the idea [10] that the embryonic PVS is like a matrix for the development of vessels and that the PVS has an early embryologic connection with the heart.

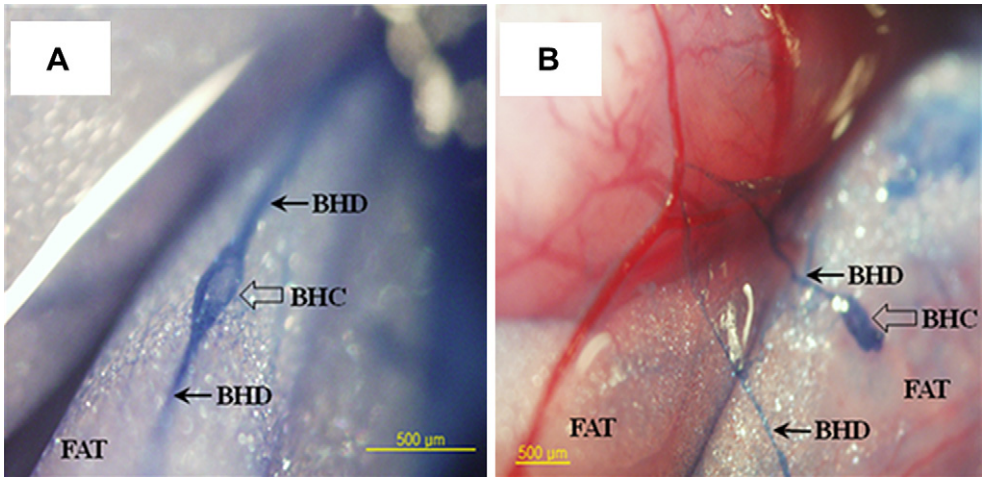

Figure 4 Trypan blue stained images of primo vascular system inside adipose tissues [12, *J Acupunct Meridian Stud*. 2009;2:93–106]. (A) primo vessel node (Bong Han Corpuscle, BHC) and vessel (Bong Han Duct, BHD) around the rat's small intestine; (B) primo vessel node and primo vessel near the small intestine of the same rat.

5. PVS role in pathological processes

The PVS is found to be connected to tumor tissues growing in internal organs as well as on the fascia of tumor tissue [4,49,69,70]. A direct relation of the PVS to tumor tissues was found in nude mouse experiments with the injection of cancer cells. The PVS was observed in the fascia wrapping tumor tissue that grew in the skin and was visualized by using the Trypan blue method. The PVS was hypothesized to play a double role: a novel path of metastasis and control of tumor tissue via acupuncture [12]. The PVS may be utilized as a drug delivery path for cancer [55] and for repair and regeneration of tissues [10,12].

Based on experiments related to internal-organ surfaces, the PVS was conjectured to be a pathway for macrophages in adipose tissue [48]. The PVS was visualized inside adipose tissues by using *in vivo* Trypan blue staining. The PVS in adipose tissues may be a source of mesenchymal stem cells, which can be differentiated into adipocytes. Obesity is known to be associated with macrophage accumulation in adipose tissue [71]. A molecular study showed that alterations of adipose tissue and its metabolic endocrine function led to an increased release of fatty acids, hormones, and pro-inflammatory molecules that contributed to obesity-associated complications. The apparent relationships between stored fats and the PVS may provide a critical clue to identifying a potential mediator for the treatment of obesity.

Bong-Han Kim showed that a corpuscle and duct system existed throughout the whole body, including the brain. Threadlike structures have been observed in the cerebrospinal fluid of the brain ventricles and the spinal central canal of rabbits [45]. The PVS in the central nervous system, such as the brain and the spinal cord, suggests that the BH system is a potential acupuncture meridian. For a long time, the brain was believed to be incapable of regeneration after embryonic development. However, the process by which neurons are generated from neural stem and progenitor cells, now known as neurogenesis, is now known to occur even in adults. Adult neurogenesis was found in the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus. Acupuncture has long been used to treat neurologic conditions, with the point ST36 being used for treating stroke and Alzheimer's disease in Eastern countries [72]. Further studies are required to elucidate the role of the PVS connecting the skin to the brain in terms of the beneficial effects of acupuncture and its relationship to the meridian system.

6. Concluding remark

We reviewed the methodology, instruments, and subject animals used for the studies of the PVS, which is suggested to be the physical structure of the meridian system for acupuncture treatment in traditional Eastern medicine. The PVS has been observed as an anatomical system distributed throughout the entire living body. We analyzed the most important points of the PVS based on the results obtained up to now with regards to the morphological and the functional aspects thereof. Our main efforts have been directed to describing the main thesis regarding the morphological structures and their topographies, the functional mechanisms of the PVS, and possible roles of the PVs in pathological processes. The substance of the PVS in all aspects may play a critical role as a core structure covering the whole body and regulating and coordinating the biological processes that are the basis for life. We conclude that the PVS is a new integrated morphological-functional system.

Acknowledgment

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