The Neuronal Connection

15

In 1901, Christian Shiler [294] published an article in which he discussed the connection between the nervous and vascular systems. He wrote: "*In muscular and glandular tissues—and perhaps throughout the body: there is a vast peripheral nervous, plexus belonging to the capillary blood-vessels. These nerves of the capillaries, which may perhaps be regarded as nutritive nerves, regulate the production and transudation of the lymph, and are concerned in the mechanism of glandular secretion. They may influence, through their connections with the vasomotor nerves on the arteries and veins, the blood supply to a part.*" He continues: "*Lastly, if the nerves surrounding a capillary are traced towards the center, they can be seen to pass into the plexus surrounding the larger vessels. Very frequently two fibers can be found running on the walls of the capillaries, and if one compares the nerve supply of striped muscle with that of the capillaries it can be seen that the latter are far more richly supplied with nerves than is striped muscle*"; and finally: "*What is the significance of these nerves of the capillaries, what is their function? Although I am not so fortunate as to have at my command a laboratory in which I could experiment on these nerves, yet if we take into consideration the histological facts together with certain clinical observations and physiological experiments which have been made on these nerves, although without any accurate anatomical knowledge about them, we have, I think, satisfactory evidence and scientific support for the hypothesis which I shall here state briefly: These nerves, so intimately connected with the capillaries, influence the protoplasm of their walls in such a way that, according to the activity of the nerves, the transudation of lymph is increased or diminished.*"

This article is important because it proposes for the first time not only an anatomical link but also a functional link between capillaries and nerves. With regard to the lymphatic capillaries, the nerves would have a role in controlling, in a certain way, the lymphatic vessels and, more precisely, the circulation of the lymphatic fluid. However, Shiler had described this interaction only in one direction: from the nerve to the capillary, not from capillaries to nerves. Moreover, he postulated that the nerves induce vasodilation of the lymphatic capillaries to allow

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the “trans-sudation” of the lymphatic fluid, which is inaccurate in light of our current knowledge.

Theoretically, the neuron-vessel connection can take place at several levels: (1) innervation of peripheral vessels, (2) vascularization of nerves, (3) role of vessels in neuronal activity, (4) role of vascular factors in neuronal activity, and (5) the role of neuronal factors in angiogenesis.

Functional interaction is also suggested because of many similarities between the nervous and the vascular systems. Both have what is called an afferent and efferent route, with the exception of the lymphatic vessels. The afferent pathway, in the case of neurons, consists of motor neurons, whereas the efferent pathway is constituted by sensory neurons. In the case of blood vessels, the afferent pathway consists of arteries and the efferent pathway of veins.

The two systems, vascular and nervous, are also interconnected and have common trajectories of migration during development. However, factors produced by neural cells and astrocytes clearly stimulate angiogenesis. The reverse is also true because vascular cells produce molecules such as artemin that attract axons to them [295].

If these two systems have such important similarities and interconnections, the factors or receptors described in the nervous system may have angiogenic functions and, conversely, angiogenic factors such as VEGF may have effects on neurons.

15.1 Neuronal Factors as Angiogenic Factors

Neuropilins play a role in the repulsion of axons and are located at the growth cone. Shay Soker and Michael Klagsbrun (Harvard, Boston) identified these neuropilins as a co-receptor for VEGF [296]. Indeed, binding to the VEGF receptor is stabilized by neuropilins. In addition, the team of Anne Eichmann (Collège de France, Paris) showed that NRP1 was expressed on arteries and NRP2 on veins [297].

In addition, the teams of Anne Eichmann, Dean Li (University of Utah, Salt Lake City), and Patrick Mehlen (University of Lyon) have also identified neuronal repulsive factors having a role in angiogenesis. One of the factors is the netrin-1. This netrin-1 has modulatory activities in angiogenesis [298, 299]. Another example is represented by a molecule called Robo4. Rob4 belongs to the family of semaphorin receptors involved in axonal guidance and repulsion. Indeed, it has been shown that Rob4 binds netrin on the endothelial cells and is involved in guidance [300].

Ephrins are another class of molecules involved in the nervous system and neuronal morphogenesis [301]. Ephrins are molecules that remain attached to the membrane and interact with receptors called Eph. The involvement of these ephrins takes place at two levels. First, they are involved in the separation/differentiation between the arterial and venous systems. Second, they have a role in vessel sprouting.

15.2 Angiogenic Factors as Neuronal Factors

It has been shown that VEGF has very important activities in the nervous system and this by directly interacting with the neurons [302]. Indeed, VEGF is able to stimulate neuronal survival and neuronal stem cells. Moreover, it is able to stimulate neuronal migration. For example, in the spinal cord, VEGF stimulates the migration of commissural neurons and is responsible for the correct establishment of connexions at this level. Importantly, neuronal activity can also be stimulated. The activity of granular neurons is stimulated by VEGF. In our laboratory, we have shown that VEGF could also intervene in the modulation of motor neuron activity in the spinal cord [303].

Another important aspect is that expression of VEGF can be modulated by behavior. Indeed, it has been shown that VEGF can be increased in mice by stimulating learning and memory activity [304]. Thus, this would indicate that VEGF, acting through KDR, mediates the effect of environmental cues on cognition. This may be because of direct (on neurons) and indirect effects (via the vasculature).

15.3 Innervation of Blood Vessels

Small and large vessels are innervated. There are neuronal connections that take place with the blood vessels. Vascular innervation obviously has a role in the regulation of vascular tone in larger vessels (arterioles, etc.). However, the innervation could also have a trophic role and produce survival signals for the vasculature.

What are the mechanisms of this innervation? As discussed previously, it has been shown that, during development, artemin produced by smooth muscle cells was able to attract sympathetic nerves to the vascular wall [295]. More recently, the team of Anne Eichmann has shown that the Netrin-1 produced by vessels was involved in the attraction of the axons to the vessels and their innervation [305]. The team demonstrated that netrin-1 is produced by arterial Smooth muscle cells (SMC) at the onset of innervation, and that arterial innervation requires the interaction of Netrin-1 with its receptor called DCC, located on the sympathetic nerve growth cones. The blockade of netrin or its receptor leads to a severe reduction in sympathetic innervation of arterial vessels and to a defect in vasoconstriction.

It has recently been claimed that large coronary vessels are paths for distal sympathetic axons to reach the subepicardial layer of the dorsal portion of the ventricles [306]. These vessels therefore participate in cardiac innervation.

15.4 Vascularization of Peripheral Nerves

The sensory and motor nerves must also be vascularized to ensure their function. This peripheral nervous vascularization is not well-understood at the present time. However, it is of paramount importance, particularly in pathology and especially in the context of peripheral neuropathy observed, for example, during diabetes. Some of the mechanisms have begun to be better known. It appears that molecules of the hedghog family are involved [307].

Other molecules involved are angiopoietins, also of therapeutic interest. We have already encountered angiopoietin in the previous chapters. It has been shown that a stabilized version of Angiopoietin-1, called COMP-Angiopoietin-1, has the ability to stimulate vascularization of the spinal cord and peripheral nerves [308, 309]. This could find application in the treatment of alcoholic or diabetic polyneuropathies.