

HST-583
Cerebrovascular anatomy and neural regulation of CNS blood flow
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I. Brief review of human brain anatomy

The brain consists of neurons, glia, and blood vessels secured within the skull by three layers of connective tissue membrane called the meninges. The outer, tough meningeal layer is called the dura and is actually a double-layered membrane that splits to form the venous sinuses. The middle membrane is the arachnoid, it is devoid of vasculature and serves to bridge the dura, adherent to the skull, to the surface of the brain. The thin, inner-most membrane that hugs close to the surface of the brain, diving into every sulcal depth, is the pia.

The brain has no lymphatic system. It is bathed in cerebrospinal fluid (CSF), formed by specialized endothelial cells lining the ventricles, the choroid plexus. In the superior sagittal sinus, CSF is reabsorbed through specialized cells called the arachnoid granulations.

As you learned in the first module of the course, it is essentially the water (or proton) content of tissue that determines MR contrast. For the tissues in the head, neurons, glia, vasculature, CSF, meninges, skull, bone marrow, and scalp each have their characteristic appearance in an MR image that is determined by the relative T1 and T2 weighting of the image. In T1 weighted images, CSF is black, grey matter is slightly darker than white, blood vessels are white and the skull is black. In T2 weighted images, CSF is white, grey matter is slightly lighter than white, blood vessels are white and the skull is black.

Special imaging techniques (MR angiography, MRA) can be used to preferentially isolate the large diameter vasculature based on the fact that the movement of blood through them serves as an endogenous source of contrast.

II. Blood supply to the brain and cerebrovascular anatomy

Blood supply to the brain is unique in that derives from four major arteries that eventually coalesce to form an equalizing distributor- the circle of Willis. There are two paired sources, the vertebral arteries that ascend the anterior surface of the upper spinal cord and brainstem before fusing into the single basilar artery and the internal carotid arteries which each run directly into opposite sides of the Circle of Willis. Each carotid artery supplies ~40% of the total perfusion of the brain. This design feature protects from the disastrous consequences of occluding a supply vessel to the brain.

The main arteries enter the subarachnoid space and divide many times (becoming the pial vessels) before penetrating the substance of the brain to form smaller arterioles and capillaries. The smallest pial arteries enter the brain parenchyma at a right angle to the surface of the brain. There is considerable individual variability in the exact pattern of the arterial blood supply to the brain.

In humans, the capillary bed has no end arteries, so that there is free communication throughout most of the vascular tree of the brain. The capillaries form

numerous anastomoses before coming back together into venules and veins. Venous blood is drained from the brain through a set of venous sinuses and then exits by the jugular veins.

Note that the vast majority of human brain blood vessels are in the size range of “microvasculature”- that is less than 200 μm in diameter. This is true beginning from the smallest diameter pial arteries and including virtually all intraparenchymal vessels. Evidence suggests that there is relatively complete perfusion of all brain capillaries under resting conditions. Recruitment would be a consequence of increased CBF in a capillary bed.

Evidence also suggests that the capillary density and organization is not random, but is closely related to the anatomy and level of metabolic functioning of the brain region. For instance, grey matter has greater capillary density than white matter, and within grey matter, the density of capillaries parallels the density of the neuropil (site of synaptic processing). Also, certain groups of neurons in the brainstem and spinal cord receive discrete vascularization.

The single most important feature of the brain’s vasculature is the presence of the blood brain barrier (BBB) formed by the endothelial cells of the brain microvessels. Typical features include: tight continuous quintuple-layered intercellular junctions, no fenestrations, few vesicles, no fluid-filled bulk transport channels, low wall thickness (0.2 μm), a higher mitochondrial content than in other tissues and a thick basement membrane. This barrier excludes large molecules, neurotransmitters and toxins by both forming a physical barrier and by lacking the typical transport mechanisms that operate in blood vessels in other regions of the body.

The only exceptions to the BBB are sites of adaptation for specific functions such as release of neurosecretory products into the blood stream (e.g. neural lobe of the pituitary) or for chemoreceptor function (e.g. area postrema: vomiting and cardiovascular responses).

Cerebrospinal fluid (CSF) is produced by the choroid plexus found in the lateral, third and fourth ventricles. The ultra-filtrate of blood plasma circulates through the ventricles and out to the surface of the brain and is drained back into the dural venous sinuses through the arachnoid granulations. The steady rate of CSF production is 500 ml per 24 hours. CSF production and rate of re-absorption do not make a major contribution to the regulation of intra-cranial pressure.

Note that there is good evidence that human cerebrovasculature undergoes age related changes, in health and diseases such as hypertension, and atherosclerosis.

III. Neural modulation of cerebrovasculature

As in all other areas of the body, blood vessels in the brain are richly innervated by autonomic and sensory fibers. The fibers are believed to participate in the regulation of local vascular tone, in pain transmission and in the natural growth of the vessel wall.

The presence of the BBB prevents circulating catecholamines from stimulating the perivascular adrenergic receptors that are located on the outer layer of the smooth muscle.

Sympathetic nervous system activation of cerebral vasculature by release of NE and/or NPY results in constriction of the blood vessels. The primary source of sympathetic fibers to the cerebral vessels originates in the superior cervical ganglion. The fibers, containing both norepinephrine (NE) and neuropeptide Y (NPY) run in the adventitia (connective tissue that supports the blood vessel) along the internal carotid artery as a solid nerve, the internal carotid nerve. The internal carotid nerve branches to follow the branching arteries all the way to the penetrating cortical arterial and arteriolar branches. This same nerve gives off a branch that supplies the veins and venous sinuses. There is very little spread over the midline.

Sympathetic nerve fibers surround virtually all arteries, with a density that is roughly proportional to the diameter of the vessels. Cerebral arteries are among the most densely innervated for arteries of a given diameter. Small pial arteries of 100 μm or less have 2-3 fibers running irregularly along the adventitia. Single fibers can be found on arterioles as small as 15 μm in diameter. Rostral to caudal gradient in fiber density.

Parasympathetic fibers innervating the cerebral vasculature contain both acetylcholine (ACh) and vasoactive intestinal polypeptide (VIP). Parasympathetic nervous system activation of cerebral vasculature by release of ACh and/or VIP results in dilation of the blood vessels. The source of these fibers is the sphenopalatine ganglion, internal carotid ganglion, and possibly other cranial nerves. There are a few parasympathetic fibers on veins. Fibers that stain positively for the enzyme that synthesizes nitric oxide (NO) from the amino acid L-arginine (nitric oxide synthase, NOS) have been identified in cerebrovascular endothelium and perivascular fibers—mostly co-localizing with VIP suggesting parasympathetic origin.

Sensory fibers originating in the trigeminal ganglion contain calcitonin gene related peptide (CGRP), substance P (SP), and neurokinin A as putative neuropeptide neurotransmitters. The innervation is predominantly found in the large arteries at the base of the brain, pial arteries, arterioles, and veins.

IV. Modulation of cerebrovasculature by other substances

This is an area of active investigation and little absolute certainty. It is believed that local release of neurotransmitters during neural activity does not directly affect the vasculature. However, the vasculature smooth cells and pericytes are endowed with both neurotransmitter receptors and are seen to have direct synaptic contacts. There is evidence that suggests several functionally relevant, direct neural projections to vasculature including: 1) NE fibers from the locus coeruleus (LC), 2) serotonergic (5-HT) fibers originating in the raphe nuclei, and 3) ACh containing varicosities from intracortical basal forebrain projection neurons.

Unquestionably this is an area in need of further investigation.

Figures in lecture from:

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