Veterinary Bioscience: Cardiovascular System

STRUCTURE AND FUNCTION OF BLOOD VESSELS 1: PRESSURE AND FLOW IN THE VASCULAR TREE

LECTURER: DR LAURA DOOLEY

Laura graduated as a veterinarian from the University of Melbourne in 2007. She then worked in small animal private veterinary practice in Australia and the United Kingdom for 7 years. She subsequently completed her PhD in cardiovascular pharmacology, and a Graduate Certificate in University Teaching at the University of Melbourne. She is now a Senior Lecturer at the Melbourne Veterinary School, and teaches into the Bachelor of Science program as well as the first and second years of the Doctor of Veterinary Medicine program. She engages in educational research, and has a special interest in student support, curriculum development, and collaborative learning.

Email: laura.dooley@unimelb.edu.au

INTENDED LEARNING OUTCOMES

At the end of this lecture you should be able to:

- Describe the basic mechanism of contraction of vascular smooth muscle cells
- Define autoregulation of blood flow and briefly describe the myogenic response, metabolic hyperaemia and reactive hyperaemia
- Describe the intrinsic (local) and extrinsic (neuronal and hormonal) influences on arteriolar tone
- Explain the importance of the vascular endothelium in regulating vascular tone and how nitric oxide functions as a vasodilator.

KEYWORDS

Vascular smooth muscle, myosin light chain kinase, calcium, intrinsic control, extrinsic control, myogenic response, vasomotion, reactive hyperaemia, metabolic (active) hyperaemia, autoregulation, nitric oxide, endothelium.

LECTURE OVERVIEW

Differences in blood flow to organs and tissues are determined by differences in vascular resistance. As arteriolar diameter determines resistance to local flow, changes in tone (vasodilation and vasoconstriction) allow for both increases and decreases in blood flow. Vascular resistance is controlled by intrinsic and extrinsic mechanisms. Extrinsic control mechanisms act from outside the local tissue and include neuronal and hormonal influences. Intrinsic mechanisms are exerted by local tissue in response to changes in the local microenvironment, and include chemical signals such as due to paracrine signalling molecules, and those due to local metabolism.

Observed changes in blood vessel tone are an integrated response which depends on the nature and number of specific receptors on the smooth muscle and endothelium, local metabolic signals, as well as hormonal and neural signals.

Contraction and relaxation of vascular smooth muscle may be specific to the type of blood vessel and the organ in which it sits, and involves the metabolic needs of the tissue, the myogenic response to stretch, the endothelium dependent response to flow as well as extrinsic influences brought about by nerves and hormones.

SMOOTH MUSCLE CONTRACTION

The tunica media of a range of blood vessels consists mainly of smooth muscle cells. Vascular smooth muscle contraction is, like cardiac muscle, controlled by intracellular calcium concentration, however the intracellular mechanism is different.

Regulation of contraction is based on myosin: As intracellular calcium rises, it binds to a regulatory protein, calmodulin, which activates the enzyme myosin light chain kinase (MLCK). This phosphorylates myosin molecules, which then form cross bridges with actin, thus bringing about contraction. The force-length relation is qualitatively similar to that of striated muscles, so the *sliding-filament mechanism* is analogous. Myosin light chain phosphatase eventually removes the phosphate groups from the myosin heads, thus ending cycling.

Smooth muscle cells are spindle-shaped and rather small (approx 5 x 200 µm). Smooth muscle cells contain a few thick myosin-filaments, and many thin actin-filaments attached to *dense bodies*. Smooth muscle cells contain a much less developed sarcoplasmic reticulum (which can store and release Ca^{2+}) than skeletal muscle. During an action potential the inward flux of ions is not Na^{+}, but Ca^{2+} (no voltage operated Na channels). The inward movement of calcium is through voltage operated and receptor operated calcium channels.

Vascular contraction is slow but results in sustained maintenance of isometric force. Smooth muscle cells maintain large forces almost continually to produce basal degree of vascular smooth muscle contraction which is important to support arterial blood pressure. Spontaneous depolarisation leads to action potentials that produce this basal tone. Mechanical and chemical factors modify this activity, bringing about fine control.

FACTORS CONTROLLING VASCULAR TONE

EXTRINSIC MECHANISMS

Neural control of vascular smooth muscle tone

Sympathetic nerve endings innervate vascular smooth muscle and release noradrenaline, which is the major neurotransmitter influencing vascular tone. Alpha (α) adrenergic receptors on the vascular smooth muscle cell membrane mediate vascular contraction.

When α-adrenoceptors are stimulated, contraction is brought about by an intra-cellular signalling pathway. The receptor activates the G-protein (Gp or Gq), which in turn activates the enzyme phospholipase C. The enzyme cleaves membrane phospholipid to produce inositol triphosphate, which opens calcium channels on the sarcoplasmic reticulum. The modest increase in intracellular calcium then causes opening of voltage gated calcium channels which causes extracellular calcium to flood in to the smooth muscle cell.

HORMONAL CONTROL

Many circulating substances such as adrenaline, angiotensin, thromboxane A_2 and serotonin also cause contraction via various mechanisms to produce calcium influx, either as described above or via receptor gated calcium channels.

Vasodilators such as adenosine, prostacyclin and histamine cause smooth muscle cell relaxation, mainly by increasing either of the two second messengers cyclic AMP or cyclic GMP.

Beta 2 (β_2) adrenoceptors cause dilation (e.g. in blood vessels within skeletal muscles and the coronary circulation) by responding to circulating NA and adrenaline.

INTRINSIC MECHANISMS

Intrinsic mechanisms of control are mechanisms which act locally within individual tissues. Intrinsic mechanisms of control of blood flow predominate in the ‘critical’ organs including the coronary circulation and the brain. Important intrinsic control mechanisms include the myogenic response, vasoactive metabolites and endothelial secretions.

Autoregulation describes the mechanisms which maintain a constant blood flow despite a wide range of perfusion pressures. When arterial pressure rises, there will be a short initial increase in flow, but the arterioles will quickly contract, increasing resistance and reducing flow back down to the baseline level. Conversely, a fall in arterial pressure induces vasodilation which restores flow. Autoregulation is particularly important in tissues such as the myocardium, brain, kidney and skeletal muscle; and is absent in the pulmonary circulation. It plays an important role in protecting organ perfusion against fluctuations in arterial blood pressure, however it only operates within a limited pressure range and for this reason severe hypotension will cause an eventual fall in perfusion to critical organs. Autoregulation is achieved by a number of intrinsic mechanisms, including a stretch induced myogenic response (contraction), and also flow induced endothelial relaxation.

MYOGENIC RESPONSE

Arterial vessels contract when blood pressure is raised, and this response is termed the myogenic response. The myogenic response preserves organ flow in the face of changing arterial pressure and stabilises tissue blood flow and capillary filtration pressure if arterial pressure changes. This mechanism is particularly seen in small arterioles in the brain, kidney and myocardium. Conversely, a fall in blood pressure triggers a reduction in vascular tone and vasodilation.

VASOACTIVE METABOLITES

Metabolic control of blood flow is a very important control mechanism, matching blood flow to the metabolic demands of the tissue. For example, this accounts for the huge increase in blood flow through skeletal muscles during exercise. 'Metabolic hyperaemia' is the term given to the increase in tissue blood flow in response to an increased metabolic rate. Metabolic products such as CO_2, lactate, adenosine and potassium are released into the interstitial fluid, and this dilates arterioles.

The metabolic vasodilators act locally on resistance vessels within the active tissue. Low oxygen levels also dilate vessels.

'Reactive hyperaemia' is the term given to the temporary increase in blood flow to a tissue after a period where blood flow has been restricted. This response is mediated by the same metabolic control mechanisms as active hyperaemia.

ENDOTHELIAL SECRETIONS

The endothelium is an active cell layer which influences vascular tone through the production of a number of vasoactive substances. Blood vessels are maintained in a more open state by the flow of blood through them, generating 'sheer stress' on the endothelial cells lining the blood vessels (increased blood velocity increases sheer stress). This activates the endothelial cells to release factors which relax the underlying smooth muscle and dilate the artery or vein. Principal among these factors is nitric oxide (NO), a small gaseous molecule which diffuses into the smooth muscle cells and increases cGMP levels which causes vascular relaxation. As well as NO, it also releases vasodilatory prostaglandins, and mediates the actions of circulating substances such as thrombin and bradykinin. In some situations the endothelium may also produce the vasoconstrictor peptide, endothelin.

FURTHER READING

Cunningham, Klein, *Textbook of Veterinary Physiology*, 4th Edition, 2007. Berne RM & Levy MN, *Cardiovascular Physiology,* 6th Edition, 2008