Regulation of Perfusion 5.11

Learning Objectives

- Write an equation that expresses capillary pressure in terms of arteriolar resistance and venule resistance
- Define vasoconstriction and venoconstriction
- Describe how MLCK and MLCP regulate the phosphorylation of myosin light chains in vascular smooth muscle
- Distinguish between electromechanical coupling and pharmacomechanical coupling
- Describe Ca^{2+} sensitization
- Describe the mechanism of sympathetic vasoconstriction
- List four classes of intrinsic control of arteriolar caliber
- give two classes of extrinsic control of arteriolar caliber
- Describe the myogenic response
- Describe the effects of endothelial secretions on arteriolar caliber
- Describe metabolic control of arteriolar caliber
- Describe the effects of hormones epinephrine, vasopressin, angiotensin, and natriuretic peptide on arteriolar caliber

FOR ANY GIVEN INPUT PRESSURE, THE CALIBER OF THE ARTERIOLES CONTROLS PERFUSION OF A TISSUE

In Chapter 5.9, we saw that flow through a vessel is driven by the pressure gradient, steeply depends on the radius of the vessel, and that the major pressure drops occur in the resistance vessels, the small arteries and arterioles. In Chapter 5.10, we saw that terminal arterioles supply a set of capillaries that exchange nutrients, waste, heat, and signals with the tissues. Increasing the proportion of open capillaries by increasing the number of open arterioles enhances flow-limited transfer of materials. The caliber of the arterioles thus determines tissue perfusion. The arterioles are invested with vascular smooth muscle whose constriction or dilation regulates perfusion. This chapter is concerned with how constriction or dilation of the arterioles occurs and their consequence for perfusion and capillary pressure.

VASOCONSTRICTION DECREASES CAPILLARY PRESSURE

Figure 5.11.1 shows terminal arterioles branching into capillaries, which then collect again to form venules. What determines the pressure in the capillaries? We can approximate this answer by lumping resistance terms together. Capillary pressure decreases slightly along the capillary so there is no single capillary pressure. But we can choose some point in the capillary and ask what the pressure is in that place. Let the total flow through the arterioles be Q_{VA}. Because net filtration of plasma is small, Q_{VA} is nearly the same as the aggregate flow through the capillaries, which is nearly the same as the aggregate flow through the veins, Q_{VV}. This is the hydraulic analogue of Kirchhoff's current law. As we have taken the aggregate flows, we also take aggregate or equivalent resistances. The arterioles obey the hydraulic analogue of Ohm's law:

$$Q_{VA} = \frac{\Delta P_A}{R_A} \quad [5.11.1]$$

where the subscript "A" denotes arterioles. The pressure difference that drives flow through the arterioles is just $P_A - P_C$, where the subscripts denote arteriole and capillary, respectively.

The flow through the venules that drain this capillary bed is the same as the flow through the arterioles. We write the relation between flow through the venules, driving force, and resistance as

$$Q_{V,V} = \frac{P_C - P_V}{R_V} \quad [5.11.2]$$

Since these flows in Eqns [5.11.1] and [5.11.2] are equal, we can combine them to solve for P_C:

$$\frac{P_A - P_C}{R_A} = \frac{P_C - P_V}{R_V}$$

$$P_A - P_C = \frac{R_A}{R_V} P_C - \frac{R_A}{R_V} P_V \quad [5.11.3]$$

$$P_C \left[1 + \frac{R_A}{R_V}\right] = P_A + \frac{R_A}{R_V} P_V$$

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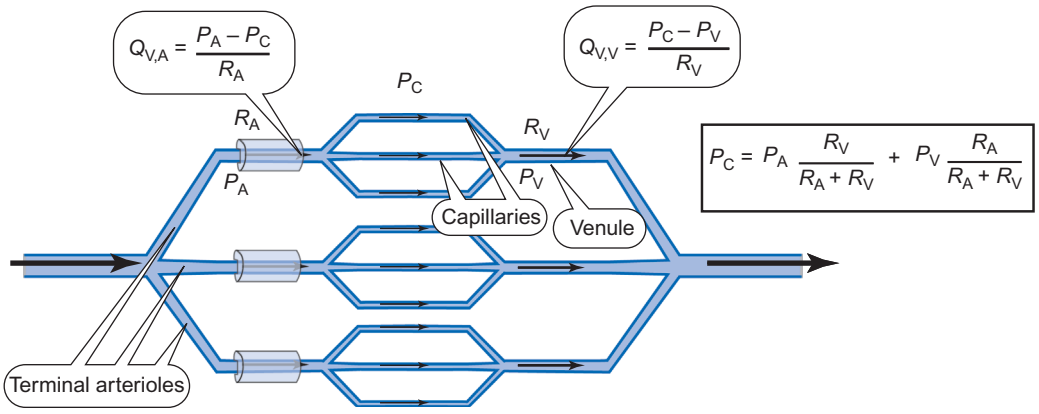

FIGURE 5.11.1 Capillary pressure is determined by the relative values of precapillary resistance, R_A and postcapillary resistance, R_V.

which leads to

$$P_C = \frac{P_A + \frac{R_A}{R_V} P_V}{1 + \frac{R_A}{R_V}} \quad [5.11.4]$$

Although this is the form of the equation as used by cardiovascular physiologists, because it expresses the resistances as a ratio, it is perhaps easier to understand if rewritten (by multiplying through by R_V) as

$$P_C = P_A \left[\frac{R_V}{R_A + R_V}\right] + P_V \left[\frac{R_A}{R_A + R_V}\right] \quad [5.11.5]$$

This hydraulic circuit is analogous to a voltage divider. Equation [5.11.5] shows that the capillary pressure must be intermediate between the arterial and venous pressures, and that its value depends on the relative resistances of the precapillary resistance, R_A, and the postcapillary resistance, R_V. **Increasing R_A lowers the capillary pressure toward P_V, and decreasing R_A raises it toward P_A.** Capillary pressure favors filtration of fluid into the interstitial space, so increasing P_C leads to edema and lowering it favors reabsorption of fluid from the interstitial space into the blood. Thus, the body reacts to **hemorrhage**, the loss of blood due to external or internal bleeding, by **vasoconstriction** mediated by the sympathetic nerves. Vasoconstriction refers to constriction of the arteries and arterioles, whereas **venoconstriction** refers to constriction of the veins. After hemorrhage, vasoconstriction raises R_A/R_V, thereby reducing P_C and favoring movement of fluid from the interstitial fluid back into the circulation.

VASCULAR SMOOTH MUSCLE CONTRACTS BY ACTIVATION OF MYOSIN LIGHT CHAIN KINASE

Most arteries have three major layers. Outermost is the **tunica adventitia**, which consists mainly of loose connective tissue, nerves, and blood vessels that supply the arterial wall. The middle layer is the **tunica media**, which contains elastic tissue and layers of vascular smooth muscle cells. Innermost is the **tunic intima**, which contains the endothelial cells that line the inner surface of the vessel and also contains elastic tissue (see Figure 5.11.2). Vascular smooth muscle cells in the tunica media control the caliber of the vessels. In vascular smooth muscle cells, force is regulated through phosphorylation of the myosin light chains, as shown diagrammatically in Figure 5.11.3.

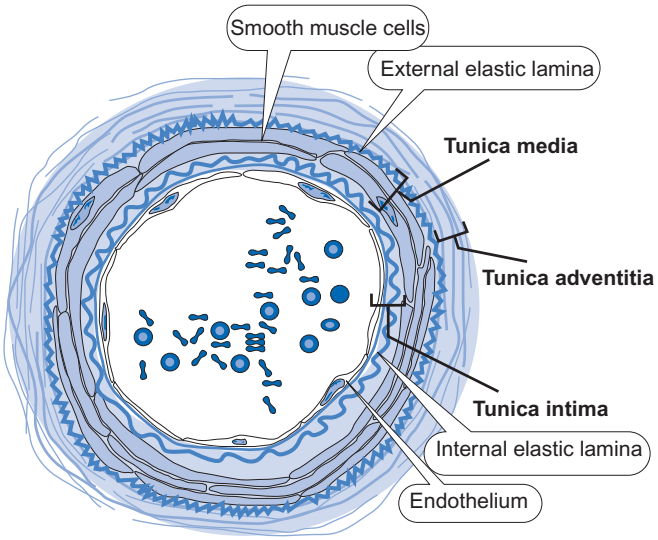

FIGURE 5.11.2 Structure of a small artery. The outermost layer, the tunica adventitia, is largely connective tissue. Inward is the middle layer, the tunica media, containing an outer layer of elastic fibers and a layer of smooth muscle cells. The innermost layer is the tunic intima, consisting of the internal elastic lamina and the endothelial cell layer that lines the lumen of the vessel.

MULTIPLE SIGNALS REGULATE THE ACTIVITY OF MLCK AND MLCP

Unlike both cardiac and skeletal muscle, there is no troponin C in smooth muscle to regulate acto-myosin interaction directly. Instead, the contractile elements themselves must be activated either by **electromechanical coupling** or by **pharmacomechanical coupling**. In electromechanical coupling, depolarization of the smooth muscle cell opens voltage-gated Ca^{2+} channels on the surface membrane (**sarcolemma**) that allows Ca^{2+} to enter the cell and raise cytoplasmic $[Ca^{2+}]$. The increased $[Ca^{2+}]$ binds to calmodulin, which then activates myosin

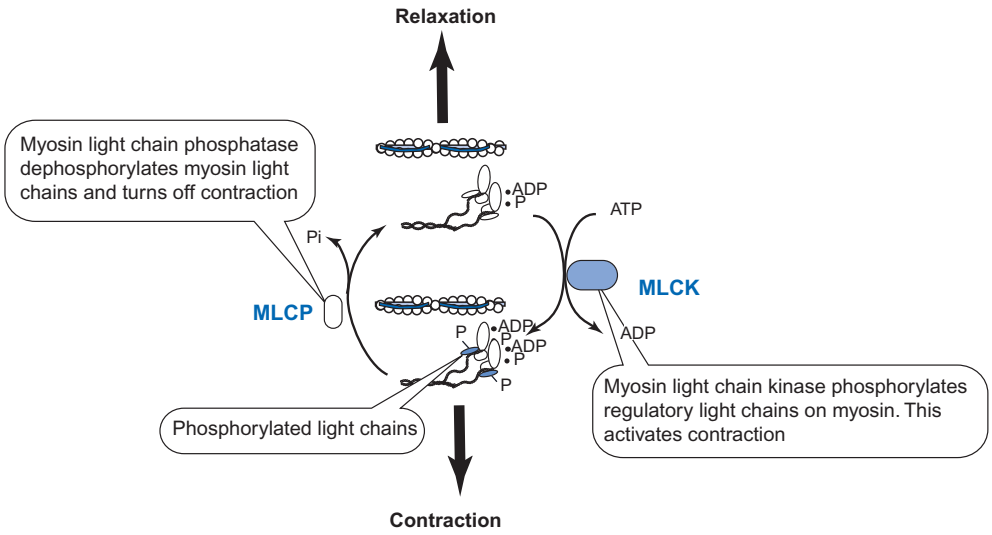

FIGURE 5.11.3 Regulation of vascular smooth muscle contraction by myosin light chain phosphorylation and dephosphorylation.

light chain kinase (**MLCK**). In pharmacomechanical coupling, chemical signals such as norepinephrine released from postganglionic sympathetic nerves bind to receptors on the sarcolemma and activate signaling systems that eventually raise cytoplasmic [Ca^{2+}]. Norepinephrine released from sympathetic terminals binds to **α_1 receptors** on vascular smooth muscle, which is linked to a **G_q** mechanism (see Chapter 2.8). Mechanisms of activation of contraction are shown in Figure 5.11.4.

Inhibition of MLCP has the same effect as activation of MLCK in that it increases phosphorylation of the myosin light chains, but this effect does not depend on Ca^{2+}. Increasing myosin phosphorylation by inhibition of MLCP is called **Ca^{2+} sensitization**, because it causes more force at any given cytoplasmic [Ca^{2+}]. There are several ways to inhibit MLCP, as shown in Figure 5.11.5. One is by phosphorylation of **CPI-17** by protein kinase C (PKC) that is activated by diacylglycerol (DAG) liberated when phospholipase C splits phosphatidylinositol bisphosphate. This is part of the G_q-coupled mechanism elicited by norepinephrine acting on α_1 receptors. A second pathway is through activation of $G_{12/13}$-coupled receptors to activate a GTP-exchange factor that converts rhoA-GDP to membrane-bound rhoA-GTP. **RhoA** is a monomeric G-protein that binds to and hydrolyzes GTP. RhoA-GTP activates rhoA kinase, a protein kinase that phosphorylates MLCP. Phosphorylation of MLCP inactivates it, thereby preserving the phosphorylation state of the myosin light chain. This mechanism is used by **endothelin-1** acting on **ET-A** receptors on vascular smooth muscle.

MULTIPLE MECHANISMS CAUSE VASODILATION

GS MECHANISMS RELAX VASCULAR SMOOTH MUSCLE

Circulating epinephrine causes vasodilation of some vascular beds, due to β_2 receptors on the vascular smooth muscle cells. These beds include skeletal muscle and myocardium. Both β_1 and β_2 receptors are linked to heterotrimeric G-proteins that are G_s-proteins which activate **adenylyl cyclase**. Adenylyl cyclase converts ATP to **3′,5′-cyclic AMP**, usually denoted as **cAMP**, that activates **protein kinase A**, or **PKA**. PKA phosphorylates several proteins in the vascular smooth muscle cell including **phospholamban** and **SL K^+ channels**. These mechanisms are shown in Figure 5.11.6.

Phospholamban is a 5 kDa protein in the SR that associates as pentamers and contains multiple phosphorylation sites. Phosphorylation of phospholamban increases the affinity of the Ca^{2+} pump on the SR so that the SR takes up Ca^{2+} more quickly, thereby relaxing the muscle by removing activation of MLCK.

PKA phosphorylates K_{ATP} channels and K_{Ca} channels in the sarcolemma. K_{ATP} channels are inhibited by ATP. Thus, they open when cells are metabolically challenged, causing hyperpolarization and no electromechanical activity. K_{Ca} channels are activated by elevated cytoplasmic [Ca^{2+}], causing vasodilation. Phosphorylation of the K^+ channels increases their outward currents, reducing the excitability of the cells.

NITRIC OXIDE RELAXES VASCULAR SMOOTH MUSCLE BY STIMULATING GUANYLATE CYCLASE

A variety of agonists and physical forces cause endothelial cells to form **nitric oxide**, **NO**. As described in Chapter 3.8, three different enzymes convert L-arginine and O_2 to NO and citrulline. These include the endothelial nitric oxide synthase (**eNOS**), the neuronal NOS (**nNOS**), and an inducible NOS (**iNOS**). NO produced by the endothelial cells diffuses to the vascular smooth muscle where it relaxes the cells. The early name for NO was **e**ndothelium **d**erived **r**elaxing **f**actor, or EDRF.

NO activates a **soluble guanylate cyclase** that increases **cGMP** in the cells. This in turn activates **protein kinase G (PKG)** that phosphorylates target proteins. PKG phosphorylates phospholamban, the protein that regulates

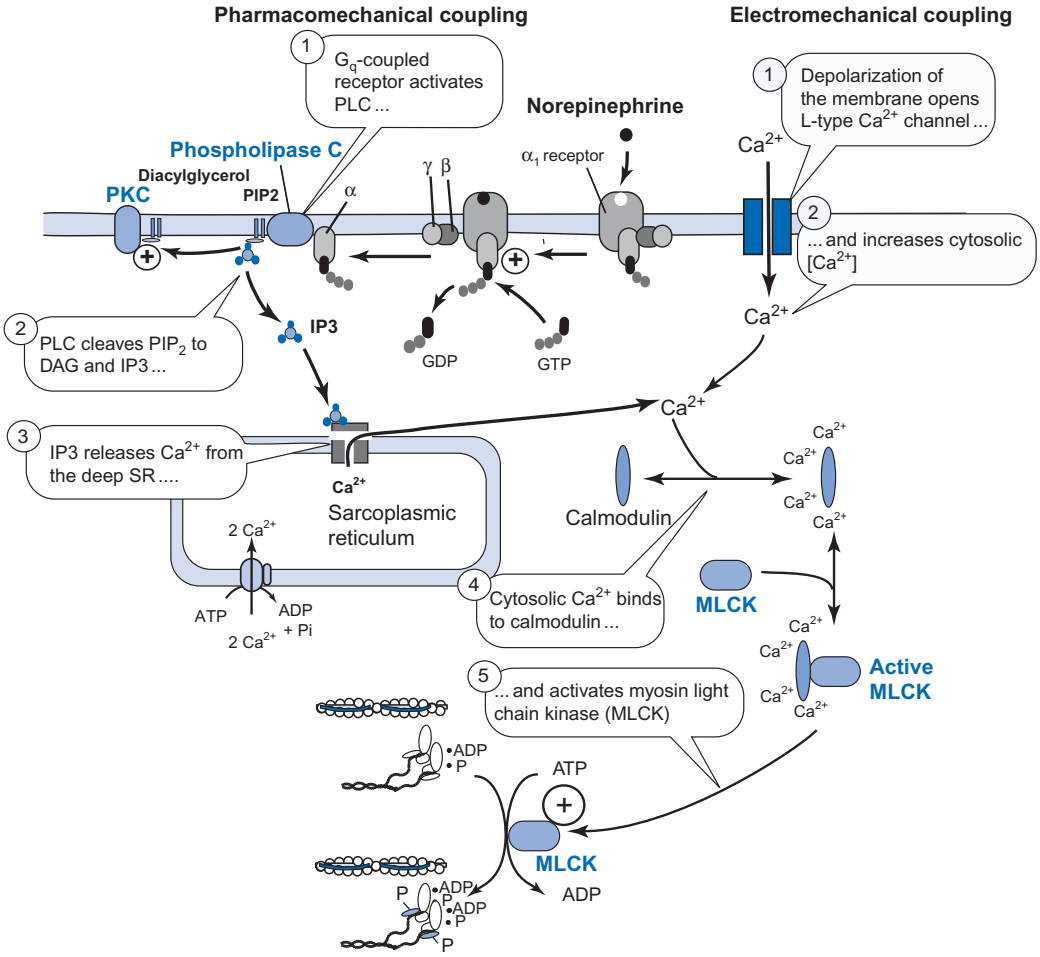

FIGURE 5.11.4 Electromechanical coupling and pharmacomechanical coupling in vascular smooth muscle cells. In electromechanical coupling, cytoplasmic [Ca^{2+}] rises because voltage-gated Ca^{2+} channels open in response to membrane depolarization; the cytoplasmic Ca^{2+} binds to calmodulin and activates MLCK. MLCK phosphorylates the myosin light chains and activates actin–myosin interaction and contraction. In pharmacomechanical coupling, cytoplasmic [Ca^{2+}] rises by IP3-induced release of Ca^{2+} from SR stores. IP3 arises from G_q-coupled activation of phospholipase C.

SERCA2a in the SR membrane, thereby increasing Ca^{2+} uptake and bringing about relaxation by removing activation of MLCK. PKG also stimulates MLCP activity, thereby reducing the phosphorylation of the regulatory light chains and decreasing Ca^{2+} sensitivity. The effects of NO are integrated into Figure 5.11.6.

CONTROL OF BLOOD VESSEL CALIBER IS LOCAL (INTRINSIC) AND SYSTEMIC (EXTRINSIC)

Many different physiological agents control blood vessel constriction or dilation. These are broadly classified as **intrinsic** and **extrinsic**. Intrinsic control refers to control that originates within the tissue being perfused. Extrinsic control refers to control that is imposed on the vascular bed by control systems that reside outside the organ being perfused. Each of these broad classifications have several classes of control.

INTRINSIC CONTROL

- myogenic response;
- endothelial secretions (NO, prostacyclin, endothelin);
- metabolic control (adenosine, acid pH, K^+);
- local paracrine secretions (histamine, bradykinin, prostaglandins, thromboxane, serotonin).

EXTRINSIC CONTROL

- nerves;
- hormones (epinephrine, vasopressin, angiotensin, atrial natriuretic peptide (ANP)).

THE MYOGENIC RESPONSE ARISES FROM THE CONTRACTILE RESPONSE TO STRETCH

William Bayliss discovered the myogenic response in 1902 when he found that distension of blood vessels by increased blood pressure caused their contraction. Thus, the myogenic response results from stretch-induced

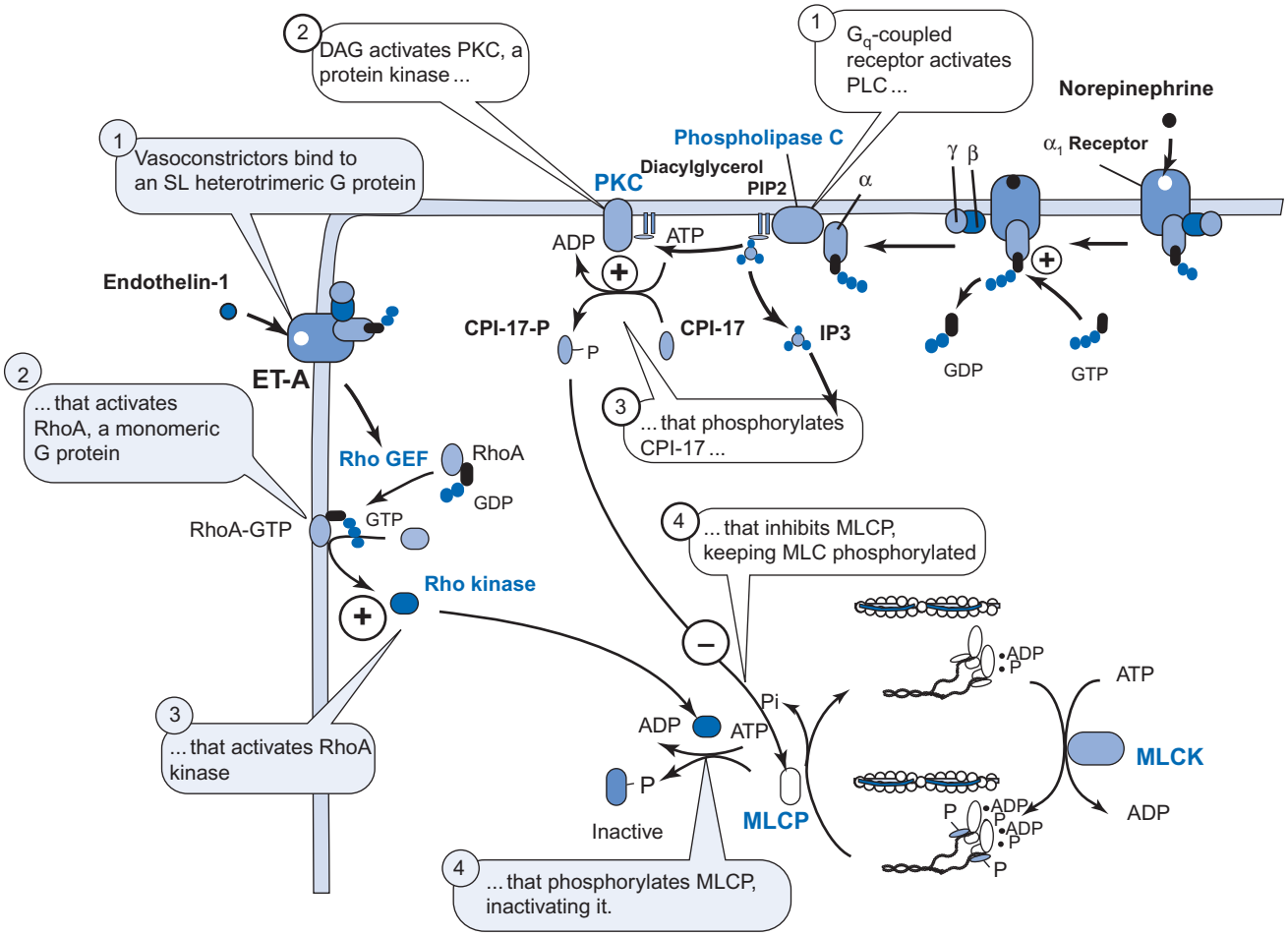

FIGURE 5.11.5 Mechanisms of Ca^{2+} sensitization. See text for description.

contraction. Its mechanism is not thoroughly known, but probably involves stretch-activated cation channels that depolarize the cells, thereby opening voltage-gated Ca^{2+} channels. Volume-regulated Cl^- channels may also be involved. Maintenance of stretch-induced vasoconstriction for long periods appears to involve a vasoconstrictor, 20-HETE (20 hydroxy eicosa-tetra-enoic acid), a hydroxylated derivative of arachidonic acid. This vasoconstrictor helps prevent repolarization of the cell, thereby maintaining its contraction.

ENDOTHELIAL SECRETIONS DILATE ARTERIOLES

Endothelial cells produce at least three substances that affect blood vessels: **NO**, **prostacyclin (PG_{12})**, and **endothelin**. NO and prostacyclin are vasodilators, whereas endothelin is a vasoconstrictor. All three substances are secreted as they are synthesized—they are not stored for later release.

NO is synthesized by **eNOS** converting L-arginine + O_2 to citrulline + NO. Agonists such as thrombin, bradykinin, substance P, and acetylcholine stimulate NO production by endothelial cells. Blood flowing past the surface of the endothelial cells exerts a shear stress on the cells that is proportional to the gradient of velocity normal to the surface (dv/dr is the **shear rate**). This shear stress produces a continuous, basal rate of NO production. During exercise, the increased blood flow increases the shear rate and induces vasodilation. This is called **flow-induced vasodilation**. NO vasodilates vessels by activating soluble guanylate cyclase, as shown in Figure 5.11.6.

The enzyme **cyclooxygenase** (COX) produces **prostacyclin** by acting on arachidonic acid in the cell membrane. Arachidonic acid is a 20:4 ω-6 fatty acid found in cell membranes. It is released from its phospholipid by **phospholipase A_2**. It is converted to a variety of active substances including thromboxane, prostacyclin, and 20 HETE, as described above for the myogenic response. The chemical structures of these compounds are shown in Figure 5.11.7.

Endothelin is a 21 amino acid peptide secreted by endothelial cells in response to hypoxia, angiotensin II, vasopressin, and thrombin. There are three isoforms: ET-1, ET-2, and ET-3. They mediate their effects through endothelin receptors, ET_A, ET_{B1}, ET_{B2}, and ET_C.

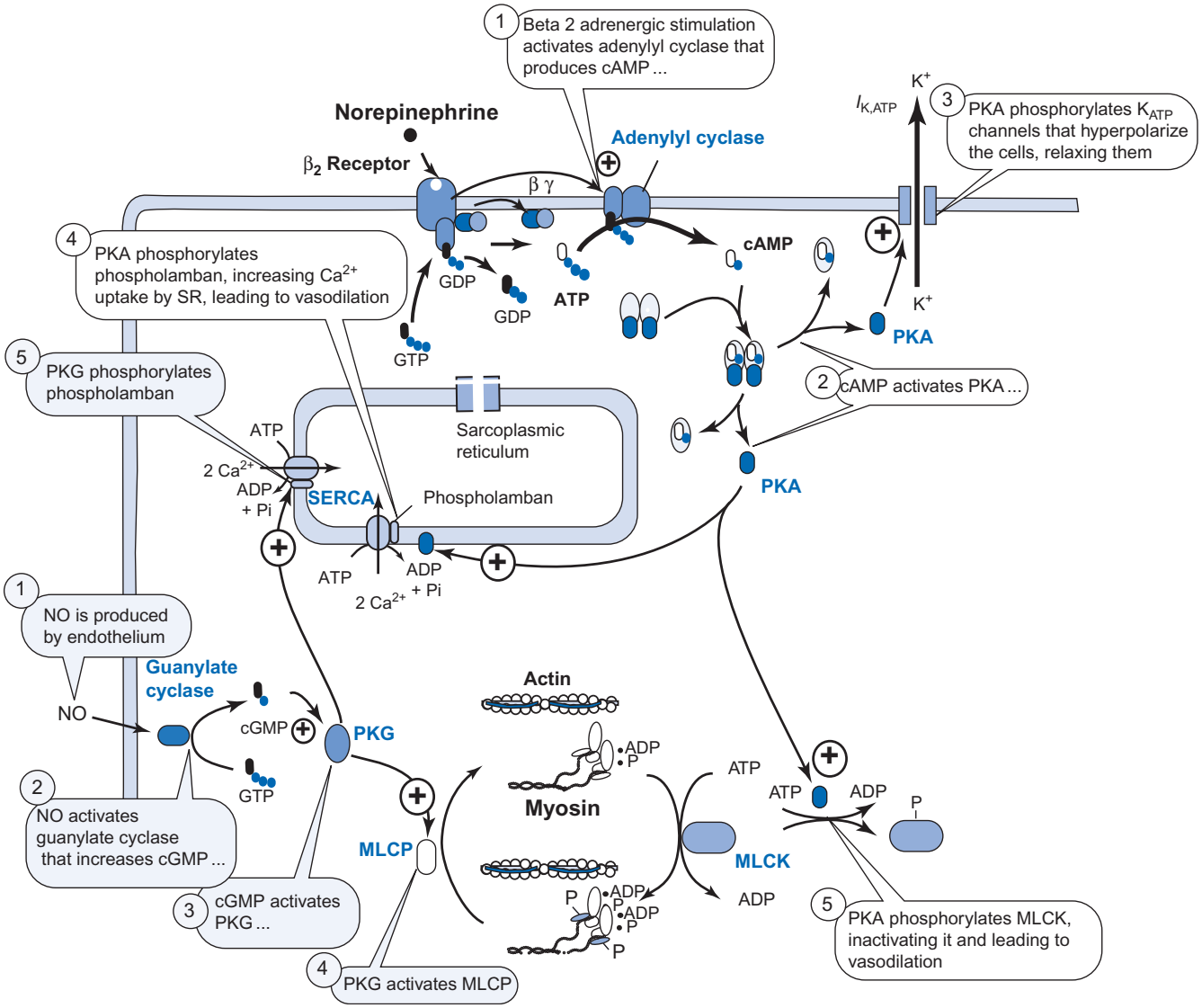

FIGURE 5.11.6 Mechanism of vasodilation. Reduction in the level of phosphorylation of the myosin regulatory light chain brings about relaxation. Activation of β_2 receptors activates adenylyl cyclase that increases cytoplasmic cAMP levels. This activates PKA, which phosphorylates K_{ATP} channels on the surface membrane, which hyperpolarizes the cell and reduces Ca^{2+} influx into the cell. Phosphorylation of phospholamban increases Ca^{2+} uptake into the SR and reduces cytoplasmic $[Ca^{2+}]$, thereby relaxing the cell. Phosphorylation of MLCK inactivates MLCK activity, thereby reducing the phosphorylation state of the myosin light chains. Nitric oxide (NO) produced in endothelial cells activates guanylate cyclase, which increases cGMP, which in turn activates PKG. PKG phosphorylates phospholamban with similar results as with β_2 stimulation. PKG also activates MLCP, thereby reducing the phosphorylation of the light chains.

METABOLIC PRODUCTS GENERALLY VASODILATE

Increased metabolism of skeletal muscle, cardiac muscle, or regions of the brain causes increased blood flow to that region. This is the basis of **functional magnetic resonance imaging** of the brain (fMRI), which actually monitors blood flow to regions of the brain when they alter their activity. The response is called **metabolic hyperemia** or **functional hyperemia**. Vasodilators released from metabolizing tissue diffuse out of the tissue to the tunica media of the vessels and cause vasodilation. These vasodilators include **adenosine**, $\mathbf{CO_2}$, and $\mathbf{K^+}$. The response is extremely sensitive, so that usually oxygen delivery is directly proportional to oxygen demand (Figure 5.11.8).

During high rates of energy consumption, cells rapidly break ATP down to ADP and Pi. The ATP is regenerated in a variety of ways: muscle cells use creatine phosphate and creatine phosphokinase to regenerate ATP quickly. Myokinase generates ATP from 2 molecules of ADP in the reaction $2ADP \rightarrow ATP + AMP$. Some of this AMP leaks out of the cells where AMP 5′ nucleotidase breaks it down to

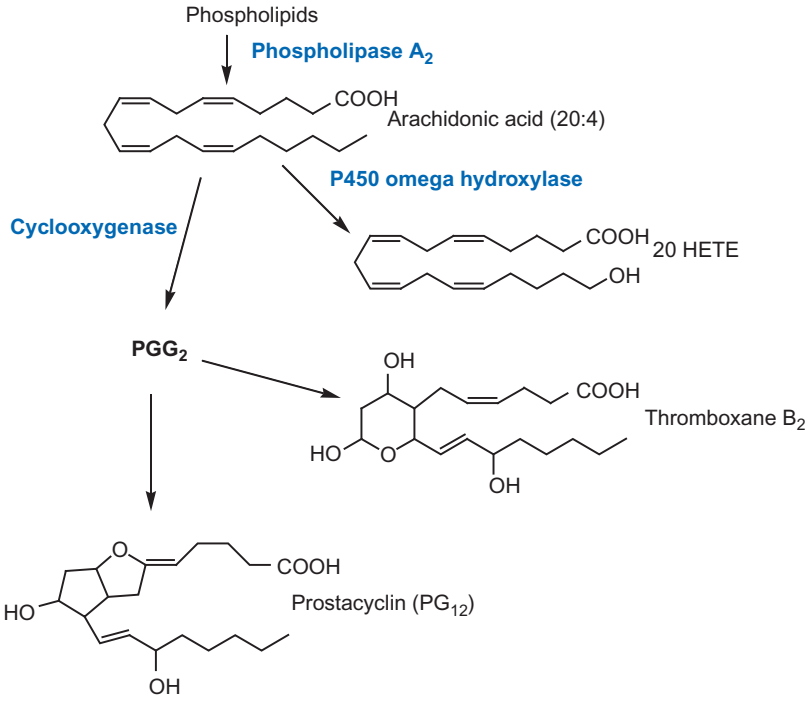

FIGURE 5.11.7 Chemical structures of arachidonic acid, 20-HETE, thromboxane B_2 and prostacyclin.

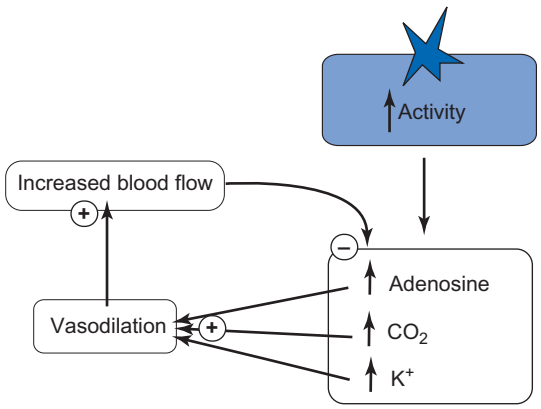

FIGURE 5.11.8 Metabolic vasodilators. Increased activity results in increased levels of adenosine, CO_2, and K^+. These all cause vasodilation, which increases blood flow and washes out the metabolites and in some cases reduces their production by increased O_2 supply.

adenosine. This extracellular adenosine binds to receptors that ultimately cause vasodilation. Adenosine causes only part of the metabolic hyperemia, because about half of the effect persists when adenosine receptors are blocked.

To regenerate ATP through oxidative phosphorylation, metabolism produces CO_2. This combines with water to form carbonic acid, a process that is catalyzed by the enzyme carbonic anhydrase. The carbonic acid dissociates to form H^+ and HCO_3^-. The increased $[H^+]$ causes vasodilation, particularly in cerebral blood vessels. The effect is less pronounced in cardiac and skeletal muscle.

Increased activity of muscle or nerves means increased frequency of action potentials, and each action potential entails an inward Na^+ current to depolarize the cell and an outward K^+ current to repolarize it. During rest, the Na^+–K^+-ATPase restores the Na^+ and K^+ to their proper compartments, but during activity it cannot keep up. The $[K^+]$ outside the cell increases. Ordinarily you would expect this to raise E_K and depolarize the cell, but in the range of increased interstitial fluid $[K^+]$ (4–9 mM), an inwardly rectifying K^+ channel is activated, causing hyperpolarization of vascular smooth muscle cells and vasodilation.

PARACRINE SECRETIONS AFFECT VASCULAR CALIBER

Local paracrine secretions that affect vascular smooth muscle include **histamine**, **bradykinin**, **thromboxane**, **prostaglandins,** and **serotonin**.

Histamine is a major mediator of **inflammation** (see Chapter 5.2). Mast cells and basophilic leukocytes synthesize and store histamine, and release it in response to trauma and allergic reactions such as **urticaria** (hives), **asthma**, and **anaphylaxis**. Histamine dilates arterioles, constricts veins, and increases capillary permeability. The different effects on arterioles and venules are mediated by different receptors. H1 receptors link to a G_q mechanism that raises cytoplasmic $[Ca^{2+}]$ and ultimately causes venoconstriction and increased vascular permeability. H2 receptors are linked to

a G_s mechanism that increases cAMP in smooth muscle cells and ultimately causes relaxation and vasodilation.

During inflammation, the enzyme kallikrein is activated by proteolytic fragments of clotting factor XII. Kallikrein then cleaves kininogen to form a 9 amino acid fragment, **bradykinin**. Bradykinin contributes to the vasodilation and tissue swelling and it produces pain.

Thromboxane A_2 and **prostacyclin** are both produced from arachidonic acid in a cascade involving **cyclooxygenase**. This enzyme is the site of action of the **nonsteroidal antiinflammatory drugs (NSAIDs)** such as aspirin, ibuprofen, and indomethacin. Thromboxane A_2 is released by platelets upon contact with collagen. Its potent vasoconstriction helps stop bleeding and also helps aggregate the platelets to form the platelet plug. Prostacyclin, on the other hand, is a vasodilator.

Platelets also release serotonin as part of the normal clotting reaction. Its vasoconstriction assists in the arrest of bleeding.

THE SYMPATHETIC NERVOUS SYSTEM PREDOMINANTLY CONTROLS THE VASCULAR SYSTEM

The sympathetic nervous system provides the main innervation of vascular smooth muscle. It releases norepinephrine at varicosities near the smooth muscle cells. The effects of the norepinephrine depend on the receptors on the vascular smooth muscle. Those having α_1 receptors activate a G_q-protein that ultimately constricts the smooth muscle by increasing cytoplasmic $[Ca^{2+}]$. Those having α_2 activate a G_i-protein that also constricts the smooth muscle by decreasing [cAMP] within the cells. Other smooth muscle cells have β_2 receptors that cause vasodilation by increasing [cAMP]. The α and β receptors derive their description from the relative potency of norepinephrine, released from sympathetic nerve terminals, and epinephrine, released from the adrenal medulla. Vascular smooth muscle in skeletal muscle contains mainly β_2 receptors that dilate upon exposure to epinephrine or norepinephrine. Vascular smooth muscle in the intestines and skin have mainly α_1 receptors and constrict upon sympathetic stimulation.

In most vessels, the sympathetic nervous system provides tonic activity. For tissues such as the skin and intestine, which constrict in response to sympathetic stimulation, vasodilation is accomplished by removal of tonic sympathetic activity.

In a few tissues, the vascular smooth muscle is innervated by parasympathetic nerves that dilate the vessels. These tissues include the salivary glands, some gastrointestinal glands and the erectile tissue of the external genitalia. The postganglionic parasympathetic fibers to these tissues release acetylcholine onto endothelial cells which are activated by it to produce NO.

CIRCULATING HORMONES THAT AFFECT VESSEL CALIBER INCLUDE EPINEPHRINE, ANGIOTENSIN, ANP, AND VASOPRESSIN

EPINEPHRINE ORIGINATES MAINLY FROM THE ADRENAL MEDULLA

Preganglionic sympathetic fibers originating in the thoracic spinal cord travel through the paravertebral ganglia and celiac ganglia to reach the adrenal medulla. There they synapse on specialized cells, the **chromaffin cells**, in the adrenal medulla. These cells are ganglionic sympathetic neurons. They have nicotinic acetylcholine receptors on their membranes and respond to sympathetic stimulation by secreting epinephrine and norepinephrine into the blood, in a ratio of about 3 epinephrine:1 norepinephrine. The effects of these on the target tissues depends on the receptors. In general, α receptors respond best to norepinephrine and β receptors respond better to epinephrine. The main stimuli for adrenal medulla secretion are exercise, hypoglycemia, hypotension, and the alerting response (the "fight or flight" reaction).

VASOPRESSIN CONSTRICTS BLOOD VESSELS

Vasopressin is also known as **antidiuretic hormone**, **ADH**. These names describe its major actions, which is to constrict the blood vessels and reduce urine output, respectively. Its synthesis and secretion is described in detail in Chapter 9.2 and its renal mechanism is detailed in Chapter 7.6. Briefly, ADH is a 9 amino acid peptide synthesized in cells in the supraoptic nucleus and paraventricular nucleus of the hypothalamus. It travels down axons to be released in the posterior pituitary in response to **hypovolemia** or increased **plasma osmolarity**. Its actions are to limit urinary excretion of water so as to help counteract hypovolemia by not losing more fluid. This action retains water but not salt, so that the end result of vasopressin is the excretion of a highly concentrated urine. This compensates for increased plasma osmolarity by discarding salt in the urine in excess of water.

The actions of vasopressin are mediated by V1a, V1b, and V2 receptors. V1 receptors on blood vessels use a G_q-coupled mechanism that ultimately raises cytoplasmic $[Ca^{2+}]$ to induce contraction. In the kidney, vasopressin activates V2 receptors that couples a G_s receptor mechanism to insertion of aquaporin channels into membranes of the renal tubule cells. This increases water reabsorption from the incipient urine.

ANGIOTENSIN II CONSTRICTS BLOOD VESSELS, INDUCES THIRST, AND RELEASES ADH AND ALDOSTERONE

The control of circulating levels of angiotensin begins with secretion of **renin** by the afferent arterioles in the

glomeruli of the kidney. It constitutes part of the **renin–angiotensin–aldosterone (RAA)** system and is discussed in detail in Chapter 7.6. Renin is secreted in response to three inputs:

1. Renal sympathetic nerves stimulate renin release.
2. Decreased distal tubule load of Na^+ increases renin release.
3. Decreased afferent arteriolar pressure increases renin release.

The released renin cleaves a protein in the plasma, **angiotensinogen**, to form angiotensin I, a 10 amino acid peptide fragment. **Angiotensin converting enzyme**, **ACE**, cleaves off 2 more amino acids to form angiotensin II. Angiotensin II exerts several effects, including:

- vasoconstriction;
- release of aldosterone from the adrenal cortex;
- increasing the sensation of thirst;
- release of ADH.

All of these effects are designed to counteract the original stimulation for renin release, and multiple negative feedback loops are found in the system (see Chapter 7.6).

ANP OPPOSES THE RAA SYSTEM

ANP is a 28 amino acid hormone that is released by the atrium and induces a **natriuresis**. Natriuresis is increased urinary excretion of Na^+. Stretch of the atrial wall caused by high cardiac filling pressures induces ANP release. ANP stimulates renal salt and water excretion to rid the body of this excess volume. In addition, ANP exerts moderate vasodilatory effects. The consequence of this is to lower blood pressure but also to increase capillary pressure. This increases the flow of fluid out of the capillaries into the interstitial compartment. This temporarily unloads the excess vascular volume by shifting it to the interstitial fluid, and more permanently by increasing urine volume.

SUMMARY

"Perfusion of tissues" means the blood flow through the tissue. Perfusion is determined by the pressure difference between the input arterial pressure and the output venous pressure, and the resistance. The resistance in turn is determined by the caliber of the vessels, approximately in accord with Poiseuille's law. Constriction of the arterioles decreases perfusion and dilation increases it. Venoconstriction can also influence flow and capillary pressure.

Vascular smooth muscle must be activated to contract. Smooth muscle controls the interaction between myosin and actin by the phosphorylation state of regulatory light chains on the myosin, instead of by Ca^{2+} binding to troponin C as is done in skeletal muscle and cardiac muscle. MLCK phosphorylates the regulatory light chains, and myosin light chain phosphatase (MLCP) dephosphorylates them. The balance between these two reactions sets the phosphorylation state and the contractile force of the muscle.

Contraction is initiated by increased cytoplasmic $[Ca^{2+}]$ either by increasing influx into the cell through voltage-gated Ca^{2+} channels by depolarizing the cell membrane (electromechanical coupling), or by increasing Ca^{2+} influx into the cytoplasm through receptor-operated channels or by Ca^{2+} release from internal stores in the sarcoplasmic reticulum (pharmacomechanical coupling). The increased cytoplasmic $[Ca^{2+}]$ binds to calmodulin, and the Ca_4CAM complex activates MLCK.

Physiological regulation of MLCP regulates the Ca^{2+} sensitivity of smooth muscle contraction, so that high force can be elicited at low cytoplasmic $[Ca^{2+}]$ by inhibiting MLCP. $Alpha_1$ adrenergic stimulation, usually by norepinephrine, increases Ca^{2+} sensitivity by activating an inhibitor of MLCP through PKC. Other vasoconstrictors activate a monomeric G-protein called RhoA. This in turn activates RhoA kinase that phosphorylates MLCP, inactivating it.

Vasodilators exert their effects through multiple paths. $Beta_2$ adrenergic receptors, which respond to epinephrine more than norepinephrine, activate adenylyl cyclase through a G_s-protein, increasing [cAMP]. The increased [cAMP] activates PKA that phosphorylates phospholamban, a regulatory protein on the SR membrane. Phosphorylation of phospholamban removes its inhibition of the SR Ca^{2+} pump; cytoplasmic $[Ca^{2+}]$ falls and the muscle cell relaxes. Nitric oxide (NO) produced by endothelial cells in response to shear stress or agonists activates a guanylate cyclase in smooth muscle cells that ultimately activates PKG that activates MLCP and inactivates MLCK.

Vascular smooth muscle is regulated by factors within the tissue (intrinsic regulation) and factors external to it (extrinsic regulation). Intrinsic factors include the myogenic response, in which stretch induces contraction. Endothelial secretions include NO, endothelin, and prostacyclin. Metabolic factors include adenosine, acidosis, and increased extracellular $[K^+]$. Other paracrine secretions include bradykinin, thromboxane, histamine, and prostaglandins.

Most vascular beds contain only sympathetic innervation, but there are some exceptions. The sympathetic system activates differentially, causing constriction here and vasodilation there depending on the degree of activation of the nerves and on the receptors on the vessels. Many vessels contain both α receptors that contract the vessels and β receptors that dilate them. Circulating epinephrine originates largely from the adrenal medulla and has metabolic effects as well as vasoconstrictor and vasodilator activity. Vasopressin, also called ADH, is a vasoconstrictor. It is secreted by the posterior pituitary in response to hypovolemia and plasma hyperosmolarity. Angiotensin II also vasoconstricts. ANP, secreted by atrial cells in response to stretch, vasodilates.

REVIEW QUESTIONS

1. If arterioles constrict, what happens to capillary pressure? Venous pressure? What happens to the resistance of the vessel? What happens to blood flow?
2. What kind of muscle is in the vasculature? How is its contraction regulated?
3. What enzyme activates smooth muscle? How is this enzyme activated? Is the phosphorylation state of myosin light chains regulated any other way? What inhibits this other pathway?
4. What brings about vascular smooth muscle relaxation? What effect does this have on vessel caliber?
5. What is the myogenic response?
6. What materials do endothelial cells make to influence arteriolar caliber? What does endothelin do? What is NO? What does it do? What is prostacyclin? What enzyme starts the production of prostacyclin?
7. What effects do each of the following have on vascular smooth muscle: adenosine, CO_2 and K.
8. What effects do histamine, prostaglandins, bradykinin, thromboxane, and serotonin have on vascular smooth muscle?
9. What effect does sympathetic stimulation have on the vasculature?
10. What effects do angiotensin II, epinephrine, vasopressin, and ANP have on the vasculature?