

addition, IP_3 binds specific sarcoplasmic reticulum (SR) receptors to increase calcium efflux from this storage pool into the cytoplasm.

Vascular smooth-muscle cell contraction depends on myosin light chain phosphorylation that reflects the balance between the activity of relevant kinases and phosphatases. Calcium activates myosin light chain kinase via calmodulin, augmenting myosin ATPase activity and enhancing contraction. Conversely, myosin light chain phosphatase reduces myosin ATPase activity and contractile force. Other kinase/phosphorylase combinations result in a complex regulatory network that refines vascular tone and links it to physiologic requirements.

Control of Vascular Smooth-Muscle Cell Tone The autonomic nervous system and endothelial cells modulate vascular smooth-muscle cells through similar convergent pathways. Autonomic neurons enter vessel media and modulate vascular smooth-muscle cell tone in response to baroreceptors and chemoreceptors within the aortic arch or carotid bodies and to thermoreceptors in the skin. Rapidly acting reflex arcs modulated by central inputs respond to multiple sensory inputs as well as emotional stimuli through three neuronal classes: *sympathetic*, whose principal neurotransmitters are epinephrine and norepinephrine; *parasympathetic*, whose principal neurotransmitter is acetylcholine; and *nonadrenergic/noncholinergic*, which include two subgroups—nitrenergic, whose principal neurotransmitter is NO, and peptidergic, whose principal neurotransmitters are substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and the nonpeptide, adenosine triphosphate (ATP).

Each of these neurotransmitters acts through specific receptors on the vascular smooth-muscle cell to modulate intracellular Ca^{2+} and, consequently, contractile tone. Norepinephrine activates α adrenergic receptors, and epinephrine activates both α and β receptors. In most blood vessels, norepinephrine activates postjunctional α_1 receptors in large arteries and α_2 receptors in small arteries and arterioles, leading to vasoconstriction. Most blood vessels express β_2 -adrenergic receptors on their vascular smooth-muscle cells and respond to β agonists by cyclic AMP–dependent