Blood flow to tissues is regulated by several mechanisms that alter the tone of smooth muscle in the arterioles and large and small arteries. The contribution of each mechanism varies depending upon conditions prevailing in the tissue being perfused and in the organism overall. The importance of the endothelium in blood flow regulation may be appreciated by considering it together with the other mechanisms that control flow.

**VASOCONSTRICTOR INFLUENCES**

As shown in Figure 12.1, there are several vasoconstrictor mechanisms that contribute to blood flow regulation in most organs. The *sympathetic vasoconstrictor mechanism* acts upon arteries and arterioles through release of noradrenaline (21), and in all likelihood, also by release of ATP (7) as a cotransmitter. The level of activity of this mechanism is determined centrally by feedforward command and reflex control. The *myogenic response* to elevation of intravascular pressure is a ubiquitous mechanism present in arterioles of many vascular beds (25). It is also present to a degree in certain small arteries (23). In these vessels intravascular pressure acts as a stimulus to vascular smooth muscle, causing the muscle to shorten as pressure is elevated.

**VASODILATOR INFLUENCES**

A variety of substances have been proposed as mediators of vasodilation during physiological perturbations. The evidence for some of these substances is quite compelling but for many it is not, especially the putative mediators that have been invoked to explain dilation during increases in functional activity. Among the latter group, evidence is perhaps strongest for *increased potassium in the interstitial fluid* from the parenchymal cells (secondary to cell depolarization) as the mediator of the initial phase of dilation of the arterioles (3). *Endothelium-derived relaxing factor (EDRF)* is released from the endothelium by various stimuli and has a relaxing effect on vascular smooth muscle. As described elsewhere in this volume, a variety of influences can cause release of EDRF. In addition to the vasodilator influences described above, we should
note the existence of the cholinergic vasodilator sympathetic mechanism that has been reported in whole organ studies (16) and the β-receptor in vascular smooth muscle, which can lead to dilation when stimulated by catecholamines (6). We will now consider the principal mechanisms of flow regulation in greater detail.

SYMPATHETIC ADRENERGIC CONTROL

Stimulation of the sympathetic nerves releases norepinephrine and ATP from varicosities; these transmitters act on adrenoceptors (21) and P₂ (7) purinoreceptors of vascular smooth muscle to cause constriction. There is also evidence that at high frequencies of sympathetic nerve stimulation (above 10Hz), neuropeptide Y is released and enhances this vasoconstriction (44). From recent work by Luff and colleagues (35), we are now aware that the region of the varicosity from which transmitter release occurs is closely apposed to the adjacent vascular smooth muscle, providing the possibility of high local concentrations of neurotransmitter. The nature of the receptors on the smooth muscle cell in this region is not completely clear. While there is substantial evidence for junctional alpha-1 adrenoceptors (38) and P₂ purinoreceptors (7) in arterial vessels, a low-affinity gamma adrenoceptor has also been proposed (21). Alpha-2 adrenoceptors are also present, and in the larger vessels these receptors appear to be extrajunctional (15, 56). By contrast there is recent evidence that α-2 adrenoceptors present in small arterioles of rat cremaster muscle are innervated (42). It has been proposed that vasodilator metabolites released from the tissue during periods of increased metabolic activity or reduced blood flow...