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Neurochemical Regulation of Veins

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Abstract

Neural control of the venous tone is provided by the adrenergic innervation. In some venous territories, a cholinergic innervation or a non-adrenergic non-cholinergic one were identified. Hormones are also involved in the control of venous tone. Catecholamines and angiotensin II are most important venoconstrictors. The relaxing action of estrogen and progesterone was also studied insome venous territories. Vasopressin, somatostatin, insulin, and thyroid hormones have actions in pathophysiologic states. Local control of venous tone includes: metabolic regulation; humoral control; ions and endothelium-dependent regulation through vasodilators and vasoconstrictors. Veins exhibit a less pronounced endothelium-dependent control and a different response profile to endogenous vasoactive substances than arteries. Other factors such as reactive oxygen species, cytokines, fibrinogen, thrombin, oxidized LDL (low density lipoprotein) and vasostatins also play role in venous regulation. Myogenic control of veins is less important than arterial one. Pharmacological agents can also modulate venous tone. Innervation, hormones, metabolic factors, ionic environment, humoral factors, endothelium-derived vasoactive factors, and even reactive oxygen species and cytokines act directly on venous smooth muscle and endothelial cells. In addition, to their vasoconstrictor or vasodilator actions, some of these factors may be involved in other important physiological (vascular hypertrophy, intimal hyperplasia, and venular permeability) and pathological mechanisms such as venous graft pathology or varicose veins.

Key words: Adrenergic innervation; Catecholamines; Endothelium derived vasoactive factor; Nitric oxide; Reactive oxygen species; LDL.

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Introduction

Neural control of the venous tone is provided by the adrenergic innervation. In some venous territories, a cholinergic innervation or a non-adrenergic non-cholinergic one were identified. Hormones are also involved in the control of venous tone.[1] Catecholamines and angiotensin II are most important venoconstrictors.[2,3] The relaxing action of estrogen and progesterone was also studied in some venous territories.[4] Vasopressin, somatostatin, insulin, and thyroid hormones have actions in pathophysiologic states.[5,6] Local control of venous tone includes: metabolic regulation; humoral control (which involves vasoconstrictor substances, vasodilator factors and factors with both constrictor and relaxing actions); ions; endothelium-dependent regulation (venous endothelial cells produce vasodilators – Nitric oxide, Prostacyclin ($PGI_{2)}$ and Endothelium Derived Hyperpolarising Factor (EDHF) – and also vasoconstrictors –Endothelin-1 (ET-1), Thrombaxane A2 (TxA2) and Prostaglandin H2 (PGH2).[7,8] Veins exhibit a less pronounced endothelium-dependent control and a different response profile to endogenous vasoactive substances than arteries.[9–11] Other factors such as reactive oxygen species, cytokines, fibrinogen, thrombin, oxidized LDL and vasostatins also

play role in venous regulation.[12,13] Myogenic control of veins is less important than arterial one. Pharmacological agents can also modulate venous tone.[14]

Neural control

Neuralcontrol of veins is through sympathetic control, vasomotor center and neurotransmitters released by the sympathetic nervous fibers i.e norepinephrine, adenosine triphosphate, neuropeptide Y and calcitonin gene related peptide.[2,3]

Norepinephrine

Adrenergic varicosities contain the enzymatic apparatus necessary for Norepinephrine (NE) biosynthesis, storage and release. NE is synthesized through hydroxylation of tyrosine to desoxy phenylalanine (DOPA), followed by DOPA decarboxylation to dopamine. The final step involves the 3-hydroxylation of dopamine to norepinephrine by dopamine 3-hydroxylase present in storage vesicles in adrenergic varicosities. NE enters the synaptic cleft and activates the adrenoceptors on the vascular cells. Removal of norepinephrine is by uptake in the nerve endings, degraded by the intraneuronal monoamine oxidase (MAO), diffusion to the capillaries, uptake by the effector cells and enzymatic degradation by MAO and catechol-O-methyl transferase (COMT) to inactive metabolites.[2,3] NE activates post junctional receptors mainly α1 and α2 for control of vascular tone.[1] α2 A *and* α2 Bfor arterial contraction and α2 C for venous vasoconstriction.[1]

Adenosine triphosphate (ATP)

It is released from the vesicles in the sympathetic nerve terminals, acts locally and post-junctionally being hydrolyzed by ecto ATP- ase.Induces an inward current via ligand-gated channels and causes both vasoconstriction and vasodilation. Purinoreceptors (P2X) receptors are responsible for the vasoconstrictor response and Purinorceptors (P2Y) receptors mediate the relaxing response.[15]

Neuropeptide Y (NPY)

Acts on receptors Y1 and Y2 subtypes. Y1 receptor is located mainly post-junctionally and are involved in vasoconstriction. Y2 receptors were detected at pre- and post-junctional sites and mediate the pre-junctional inhibition of norepinephrine release. [16,17]

Calcitonin gene-related peptide (CGRP)

It is contained in both adrenergic and NANC (non-adrenergic non-cholinergic) fibers distributed to different components of the cardiovascular system.[18,19]

Cholinergic Innervation

Studies have revealed two separate cholinergic systems in the vascular wall. Endothelial cells represent the intrinsic, intimal system; regulator of basal vascular tone. Perivascular autonomic nerve fibers represent the extrinsic, adventitial system. Acetylcholine (ACh) can contract and relax vascular tissue. Vasodilation being endothelium-dependent and mediated via muscarinic M3 receptors.[20,21]

Non-Adrenergic Non-Cholinergic Innervation (NANC)

ATP, VIP (vasoactive intestinal peptide), CGRP, and NO were designed as neurotransmitters released by the NANC fibers.[20,21]

Hormonal control

Hormones responsible for maintenance of venous tone are Catecholamines, Angiotensin, Estrogen and progesterone. Other hormones like (vasopressin, somatostatin, insulin, thyroid hormones)also contribute.

Catecholamines are synthesized and released from the chromaffin cells of the adrenal medulla in response to emotional stress. The most important catecholamine secreted is epinephrine.[2,3] α2 and β adrenoceptors exist on endothelial cells and contribute to the regulation of vasomotor tone. α2 adrenoceptors stimulates the release of NO.[22]

Angiotensins play an important role inrenin angiotensin system (RAS). All components of RAS except renin, are produced in several tissues, including vessel wall.[23] Angiotensinogen mRNA and protein was identified in vascular smooth muscle, endothelium, and perivascular fat. ACE was found in the adventitia, endothelial cells and vascular smooth muscle cells in culture. Angiotensin II exerts two types of effects: vasoconstriction and aldosterone release. It also causes pressor effect at very low doses.[23]

Estrogens mediates its beneficial actions via

nuclear receptors, named ERα and ERβ which decrease vascular tone, has cytoprotective action on the vascular wall, increase of HDL cholesterol, decrease of LDL cholesterol, causes inhibition of LDL-oxidation and decreases plasminogen and fibrinogen levels. The relaxing effect is caused by:increased synthesis of endothelium-dependent relaxing factors (NO, PGl2, EDHF)[4], decreased production of vasoconstrictor factors, such as endothelin[24] or superoxide anion [25], decreased calcium entry into vascular smooth muscle cells[26] and decreased α-adrenergic responsiveness in venous smooth muscle cells, thereby decreasing venous tone and contributing to the pathogenesis of varicosities[27]. There is enhancement of venous compliance after ingestion of oral estrogen-containing contraceptives and occurrence of varicose veins.[28,29]

Progesterone produce a dose-dependent relaxation mediated by a receptor-activated cAMP mechanism.[30]

Other Hormones which have a role to play include vasopressin, somatostatin, insulin and thyroid hormones. The constrictor action of vasopressin seems to be lower in veins, compared to arterial preparations, due to a low population or sensitivity of receptors sites for this peptide.[5,31] Somatostatin presents both venoconstrictor and venodilator actions. The dilator effect of somatostatin was reported in the venous portal tree. A combination of somatostatin, vasopressin, and nitroglycerin seems to be very effective in patients with portal hypertension[6,32]. Insulinplays a role in the regulation of vascular tone in human vessels, including venous tone by attenuating vasoconstrictor responses to pressor agonists and increasing the vasorelaxing effect. Mechanism of insulin-induced vasodilation are decreased vascular sensitivity to α-adrenergic agonists and an enhanced sensitivity to β-adrenoceptor agonists[33]; stimulation of nitric oxide release from endothelial cells[34,35]; activation of ATP-dependent potassium channels.[36,37] Insulin has Long term actions in vascular smooth muscle cells, such as increase of Na^+-K^+-ATP-ase and Na^+-Ca^{2+} exchanger.[38,39] Thyroid Hormones have positive inotropic and vasodilator effects.[40]

Local control

Local control of veins is achieved by Metabolic, Humoral, Ions and Endothelium derived factors. PO_2 represents an important factor in local metabolic regulation venous tone. Chronic hypoxia impairs venous smooth muscle contractility.[41] Acute hypoxia increases venous smooth muscle contractility. Anoxic constriction is mediated by ET-1 release.[7] Lowered pH and increased PCO_2 decreases smooth muscle contractility.[42] Lactateis produced by the venous wall, even in normoxic conditions; in case of local hypoxia, lactate release is elevated, because LDH (lactate dehydrogenase) subunit composition in venous tissue is better suited for transformation of pyruvate into lactate [43]. In pre-eclampsia, absence of lactate induced dilatation of placental vessels may contribute to the fetal complications due to impaired blood flow and vasospasm.[44] Adenosine is well known for itspowerful relaxing effects in vascular beds. P1-purinoceptors present an agonist potency and their activation induces changes in intracellular cAMP mechanism. ATP and ADP (adenosine diphosphate) are components of platelets and erythrocytes, and can also be released from endothelial cells and smooth muscle cells.[8] Activation of P2-purinoceptors can produce either vasoconstriction or vasodilation. Endothelial P2 receptors usually mediate relaxation via production of NO.

Humoral Control involves vasoconstrictors asangiotensin II, PGF2α, Thromboxane A2, bradykinin, histamine (H1), serotonin and vasodilators as ANP (atrial natriuretic peptide), BNP (brain natriuretic peptide), CNP (c-type natriuretic peptide), PGI2, PGE2, Bradykinin, Histamine (H2), Substance P. Angiotensins exist in vascular tissue including venous wall.[45–47] Angiotensin-converting enzyme (ACE) activity was found in the endothelium and mast cells in the adventitia of the vessel wall.[48] Angiotensin I caused a marked venoconstriction. The contractile response was inhibited by AT1 receptor antagonist losartan.[49] Angiotensin II potentiates the venoconstrictorresponse via release of NE from the nerve terminals.[50,51] Ang II, Ang III, and Ang IV produced concentration-dependent contractions. The ACE inhibitor enalaprilat augmented endothelium-dependent relaxations.[52] In varicose veins, the reactivity of venous smooth muscle to angiotensin II is impaired.[53]

Natriuretic Peptidesas ANP, BNP and CNP are encoded by genes with similar structure. They exert their affects through NP receptors. Two of them stimulating guanylate cyclase, whereas the third appears mostly as a clearance receptor. ANP (mainly synthesized within the atrial myocytes), BNP (predominantly produced in atria and brain) and CNP from the vascular endothelium is involved in the control of vascular tone.[54–56]

Venous tissue is capable of producing

eicosanoids. Both endothelium and smooth muscle take part in production of both prostacyclin and thromboxane.[57] There are two forms of COX: the constitutive form COX-I, located in the endothelial layer, a cytokine-inducible isoform, COX-2, in vascular smooth muscle by IL-1β, TNF-α, bacterial LPS (lipo-polysaccharides), growth factors, and phorbol esters. Venous smooth muscle expressed higher amounts of COX-2 than the arterial one.[58] Bradykinin can be derived from a number of different sources, including endothelium and are considered local hormones acting in a autocrine-paracrine manner. ACE inactivates bradykinin and thereby blunt sendothelium-dependent relaxations to this peptide.[59] Histamine presents venoconstrictor and venodilator actions. The H1 receptors mediate their effects via products of inositol phospholipid hydrolysis and increasing intracellular calcium. H2 receptors are coupled via Gs protein to adenylate cyclase and stimulate cAMP formation, inducing a decrease of Ca^{2+}[60]. Serotonin is mainly derived from platelets acton specific 5-HT receptors, may induce both contraction and relaxation[61–63]. The relaxing action is due to inhibition of NE release from sympathetic nerveendings, by direct vascular smooth muscle relaxation, and by release of EDRF[64]. Substance Pis an endothelium-dependent vasodilator neurokinin effect being mediated by NKI receptors.[65,66]

Ions such as Sodium, Potassium, Calcium, Magnesium, and Chloride also have a role to play in local control of venous tone.Sodium distribution is regulated by [67] Na^+- K^+ pump.[68] Na^+/Ca^{2+} exchanger transports Ca^{2+} out of the cell at expense of Na influx, which then will be removed by the Na^+- K^+ pump. Sodium also takes part in- Na^+-H^+ exchanger, Na^+/K/2Cl, and Fast sodium channels. Potassium presents important role through direct and indirect mechanisms, through the electrogenic Na^+- K^+ pump, by alterations in cell membrane permeability and bymodulation of norepinephrine release by sympathetic nerves.[69] A moderate K^+ elevation (5-10 mM) produced relaxation, while a pronounced increase, above 15 mM induced venous contraction.[70] Different types of potassium channels are Ca^{2+} activated K^+ channels (BK Ca^{2+}), ATP sensitive K^+ channels (KATP) andvoltage gated K^+ channels (KV). Calcium plays a major role in the initiation of contraction, which depends on the increase of myoplasmic concentration of Ca^{2+}.Calcium influx from the extracellular pool occurs through receptor-activated, voltage-dependent, or stretch-activated calcium channels. Release of Ca^{2+} from the sarcoplasmic reticulum is linked to binding of the second messenger IP3 (ionositol triphosphate).[71] Magnesium represents a natural calcium antagonist; it inhibits voltage-dependent, receptor-dependent, and leak channels.[72,73] Reduction of extracellular Mg^{2+} level increases Ca^{2+} influx with subsequent elevation in tension and reactivity to vasoconstrictors.[72–74]

Chloride transport across cell membrane is elicited via:co-transporters, such as Na^+-Cl, K^+-Cl, and Na^+-K^+-2Cl [75], exchangers, such as Na^+-HCO_3/ Cl and HCO_3/Cl; andchloride channels.[76]

Endothelium-Derived Factors are also responsible forshort term regulation ofvenous tone. It produces vasodilator substances, such as nitric oxide (NO), prostacyclin (PGI2) and EDHF andvasoconstrictor factors, such as endothelin-1, thromboxane A2 and prostaglandin H2.

Nitric oxide (NO) is formed from the guanidine-nitrogen terminal of L-arginine by endothelial NO synthase (eNOS). Itdiffuses into the underlying vascular smooth muscle to mediate vascular relaxation by a cGMPdependent process.[11,78] Pathophysiological use of NO are in Venous graft spasm, Primary varicose veins and, Raynaud's disease. Nitrovasodilators including Glyceryl trinitrite (GTN) and other organic nitrates, are prodrugs, acting by the release of nitric oxide.[79] The venoselectivity of these NO-donating drugs presents both advantages (efficacy in heart failure and angina therapy) and disadvantages (postural hypotension, headache).[80] Endothelium-derived hyperpolarizing factors (EDHFs) induces relaxation by reducing the open probability of voltage -dependent calcium channelsand by the activation of potassium channels on the vascular smooth muscle.[10,81] Important stimuli for ET-1 release are, hypoxia and low shear stress, vasoactive substances (epinephrine, angiotensin II, vasopressin, bradykinin), growth factors (transforming growth factor)[82], and cytokines (lL-1).[83]

Other factors involved in the modulation of venous tone are Reactive oxygen species, Cytokines, Fibrinogen, thrombin, Oxidized Low-Density Lipoprotein (ox-LDL) and Vasostatins.

Reactive Oxygen Species (ROS) are generated mainly at sites of inflammation and injury. They function as signalling molecules. At higher concentration, they can endanger all cellular macromolecules.[12] Main ROS are Superoxide Anion, Hydrogen peroxide and OH (hydroxyl ions). Major ROS producing systems include[84]: NADH/NADPH oxidases, xanthine oxidase, lipo-oxygenases; cyclooxygenase; P-450 monooxygenases; the enzymes of mitochondrial oxidation, NO synthase. Défense against ROS are superoxide dismutases

(SOD), catalasesand peroxidases.[85,86] Cytokines likeIL-1 may influence venous contractility by inducing NO synthase. Fibrinogen endothelium-dependent relaxation effect is reversed at higher concentrations of fibrinogen.[13]

Myogenic control

Venous intrinsic tone play an insignificant role in overall ability of veins to regulate vascular capacity.[14]

Pharmacological aspects

Include Venodilator Drugs, Calcium antagonists, Nitro-vasodilators, ACE inhibitors. Venotonic Drugs are derived from Aesculus hippocastannum (Horse chestnut), Ruscus aculeatus (Butcher's broom), Centella Asiatica (Gotu Kola), Bioflavinoids:Diosmin and Hesperidin.

Conclusion

Innervation, hormones, metabolic factors, ionic environment, humoral factors, endothelium-derived vasoactive factors, and even reactive oxygen species and cytokines act directly on venous smooth muscle and endothelial cells. In addition, to their vasoconstrictor or vasodilator actions, some of these factors may be involved in other important physiological mechanisms, suchas vascular hypertrophy, intimal hyperplasia, and venular permeability.

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