**Vascular Reactivity; GPCR Regulation**

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The Vascular System and Dysfunction

The heart is the first organ to develop in the embryo, with vessels developing within the third week and blood circulating after 30 days in humans, which is crucial for maintaining perfusion of the developing fetus. The adult vascular system comprises arteries, arterioles, capillaries, veins, and lymphatic vessels, which in receptors widespread a wide range of endo and exocellular signals, vital for coordinating homeostasis. Blood vessels and in particular the small arteries, are important contributors in setting peripheral resistance. Constriction or dilatation in response to endogenous signals (including the chemical messengers listed) of a large proportion of vessels within the body will affect total peripheral resistance and blood pressure.

Dysfunction of the vascular endothelium contributes to shifting the balance from vasodilatation to vasoconstriction causing hypertension and is a key hallmark of diseases such as atherosclerosis, stroke and heart failure. Cardiac disease remains a major cause of mortality and morbidity accounting for about 50% of all deaths globally. Despite the advancement of drugs that target crucial G-protein-coupled receptor (GPCR) systems, such as angiotensin AT receptor antagonists and inhibitors. This support that further targets remain to be identified and potentially could be derived from emerging transmitter systems or the remaining orphan receptors.

**GPCRs**

All GPCRs share seven transmembrane spanning domains. Vertebrate receptors can be divided into five major families based on protein sequence similarity and phylogenetic analysis: Rhodopsin Family (Class AI), Secretin Family (Class B), Frizzled Family (Class F), Frizzled Family (Class D), and the Smokehened family (Class E). GPCRs mediate vascular reactivity predominantly belonging to the first two of these families. This aim of the editor is to highlight those GPCRs that on activation by their respective ligands may function in one of three ways in blood vessels as directly activating constrictors and dilators, or indirectly activating vasodilators. The schematic illustrated here, summates the predominant functional vasomotor responses of a generalized blood vessel to be activated by specific GPCRs, with important caveats: the expression of receptors with their associated G-proteins and subsequent functional responses can vary among species, different blood vessels, and, within the same vascular bed, as to activity. The importance of these receptors is underlined with the observation that vasomotor reactivity is emerging.

**Class A**

The superfamily of seven-transmembrane-spanning GPCRs that belong to Class A is the largest and most diverse family of membrane-spanning receptors. Receptors in Class A are the major target for about one third of the currently available drugs. In the most recent list published by the TUPHAR/BPS Guide to Pharmacology, 197 receptors were listed. A Class A receptor is known to interact with available ligands or chemical messengers that include many waseoseptive compounds.

Following completion of 19% of the human genome, bioinformatics has been applied to identify all, not of the remaining genes that potentially encode yet unliganded ‘orphan’ receptors in this family. In addition to the endogenous receptors in Class A where the ligand is known, a further 89 orphan GPCRs have been proposed to exist in this category. These orphan receptors continue to be expressed in cell lines or pedigred with ligands by screening libraries of existing or novel compounds isolated from tissue.[1][2][3][4] Many new transmitters are emerging as endogenous ligands, including a number of small molecules that regulate activity in the human cardiovascular system. Activation of Class A receptors can result in vasoconstriction or vasodilation either directly or via release of endothelium-derived relaxing factors (EDRF).

**Class B**

The second group of GPCRs, Class B[5], comprises 15 receptors two of which form driven with receptor accessory protein complexes to form unique signaling systems. A number of these receptors have been implicated in vascular biology, including cell proliferation, differentiation and apoptosis, but a role in vascular reactivity has not been reported.

**Class C**

Intriguingly, the 15 Class C metabotropic receptors activated by ligands, including GABA and glutamate, can be localized prenatally to peripheral nerves but not are widely expressed in the vascular endothelium or smooth muscle.

**Friedel Family**

NC/NICMOP has classified a further eleven GPCRs belonging to a separate class of the frizzled and smoothened family.[6][7] Friedel receptors are activated by a family of cyclic-lysocytylated hist protein ligands. Receptors are widely expressed in the vascular system (as well as other organs) and have been implicated in remodeling, including cell proliferation, differentiation and apoptosis, but a role in vascular reactivity has not been reported.

**Adhesion Receptors**

Some of the 33 receptors, designated orphan, in this family may play a role in the development of the cardiovascular system or angiogenesis, but a role in vascular reactivity has not been reported.

**Vascular Endothelium, Peripheral Nerves**

The vascular endothelium is a single layer of epithelial cells that line every blood vessel in the body, and therefore is present in all peripheral blood vessels. It has no nuclei and is highly permeable, so that it can communicate with the adjacent nerve fibers and an axo-synaptic junction. Endothelial cells can communicate with one another through gap junctions and through the release of chemical signals, such as cytokines (e.g., ET-1) and nitric oxide (NO). Vascular reactivity is also mediated by the release of chemical signals that have their origin in virtually all organs in the body, in addition to hormones circulating in the plasma. The chemical messengers include the complement of the vascular endothelium. Many of these changes are mediated by GPCRs.

**Indirectly Acting Vasconstrictors**

The sympathetic nervous system, principally through the release of noradrenaline from peripheral nerves, activates smooth muscle in adrenalinergic to tonically constrict the vessel wall. They display remarkable plasticity in undergoing vascular remodeling or pathophysiological alterations in the local environment. The neurokinin A receptor, for instance, plays a role in the regulation of blood flow and therefore could be responsible for the control of cardiovascular function. In addition to regulating coagulation and thrombosis, the endothelium contributes to the control of vascular tone to respond to a range of physical, such as shear stress, and chemical messengers to preserve endothelium-derived relaxing factors, including NO, endothelium-derived hyperpolarizing factor (EDHF) and prostacyclin (PGI2). In many cases, the chemical messenger is known to cause a direct contraction of vascular smooth muscle and release of relaxing factors, causing the underlying smooth muscle cells to undergo de-differentiation, proliferation, and apoptosis.[8][9] A number of different receptors play a role in the regulation of blood flow, including the endothelin (ET) receptor, angiotensin (AT) receptor, and thrombin receptor (PAR). These receptors have been implicated in the control of vascular tone and response to chemical mediators, including thromboxane A2, serotonin, and histamine.[9][10]

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