The Endothelium

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Endothelium is anatomically recognized as a single layer of cells which lines the inside of all the blood vessels. In adults, its total weight is about 3 kg.

Following functions are attributed to the endothelium:

1. Acts as a barrier and prevents the passage of many substances contained in the blood.
2. Promotes or facilitates (actively transports) many substances like insulin, lipoproteins etc.
3. Endothelium has got metabolic functions i.e. takes up and transforms substances like noradrenaline, prostaglandins as well as serotonin released from the platelets.
4. (a) Endothelium contains Angiotensin converting enzyme (ACE) which transforms angiotensin I into potent vasoconstrictor peptide, angiotensin II.
   (b) It also breaks down kinins especially bradykinin into inactive peptides.
5. New role of Endothelium was discovered by Furchgott. et al in 1980; that was the release of:
   (a) Dilatation factors i.e. EDRF (Endothelial derived relaxing factors)
   (b) EDCF(Endothelial derived contracting factors) described by De Mey et al.

EDRF

There are three EDRFs described which cause relaxation of vascular smooth muscle.

1. Nitric oxide (NO)
2. EDHF (Endothelial derived hyperpolarizing factor)
3. Prostacyclin

1. Nitric oxide (NO)

Release of EDRF in response to acetylcholine has been demonstrated in many arteries. It has got a very short half life and is destroyed by superoxide. EDRF & NO have following similarities and hence Furchgott et. al identified it as NO:

- NO is responsible for vasodilator effects of nitrates.
- Activates the same enzymes as EDRF.
- Like EDRF, it is destroyed by free radicals.
- Endothelial cells produce NO and inhibition of NO prevents most endothelium dependent relaxation.

2. EDHF

In some of the blood vessels endothelium dependent relaxation due to vasodilator drugs including acetylcholine is associated with membrane hyperpolarization of vascular smooth muscle for which NO is not responsible. Substance responsible for this has been identified as endothelium derived hyperpolarizing factor.(EDHF) This acts mainly on small blood vessels which is opposite to the action of NO which acts mainly on large arteries.

3. Prostacyclin

It is well recognized to have vasodilator properties. It is also secreted from the endothelium. It causes relaxation of vascular smooth muscle which is additive to EDRF. As far as platelet aggregation is concerned, prostacyclin and NO are strongly synergistic and cause profound inhibition of platelet aggregation.

Factors causing release of EDRF

They include:

1. Shear stress
2. Activation of endothelial receptors which in turn acts via
   a. Hormones
   b. Autocoids
   c. Platelet products and thrombin.

1. Shear stress

An increase in flow rate accompanied by pulsation of the artery causes an equal increase in the release of EDRF which results in flow induced vasodilatation.

2. Activation of endothelial receptors

The endothelial cell membrane contains many receptors for a variety of endogenous substances. These receptors are connected with NO synthesis by various coupling proteins.

a. Hormones

The main hormones concerned are catecholamines and vasopressin.

i. Catecholamines

Adrenaline and noradrenaline cause endothelial relaxation. This response is blocked by alpha-2 adrenergic antagonists.

ii. Vasopressin (Oxytocin)

Releases EDRF by acting on endothelial V1 vasopressogenic receptors. This effect is particularly marked in cerebral arteries while lacking in peripheral circulation. This arrangement helps in preferential blood flow to the brain when the hormone is secreted in large amounts during haemorrhage.

b. Autocoids

Those which cause release of EDRF are:

1. Histamine
2. Bradykinin

Endothelial action of histamine on large arterioles accounts for vasodilatation and hence produces rubor which is the characteristic feature of histamine release. Bradykinin causes pre-capillary vasodilatation via the release of NO and EDHF.

Various neuropeptides, especially substance P also causes release of EDRF which is the result of stimulation of sensory nerves.

c. Platelet products and thrombin

Thrombin stimulates NO synthesis in endothelial cells. Platelet aggregation also triggers EDRF release via serotonin and ADP. This is of fundamental importance in preventing intravascular coagulation. Rapid vascular dilatation helps to flush the microaggregates away. The increased amount of NO exerts a negative feedback on platelet aggregation.

Diseases which effect EDRF release

1. Ageing (regenerated endothelium)
2. Reperfusion
3. Atherosclerosis
4. Hypertension
5. Heart failure
6. Cerebral vasospasm

Hypertension

In hypertension, acetylcholine induced vasodilatation is inhibited in both experimental animals and human beings. A normal endothelial action is regained when arterial pressure is reduced. This proves dysfunction in the production of EDRF in hypertension.

Enthdothelium dependent contractions.

Endothelial cells also cause release of vasoconstrictor peptide termed as endothelin.

The contractions are also blocked by cycloxygenase pathway inhibitors.

In hypertension, the EDCF mediator seems to be an endoperoxide. NO on the whole acts as an EDCF scavenger and thence prevents contraction.

A logical therapeutic strategy, therefore, is to stimulate production of EDRF. This is an important action of ACE inhibitors.

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