Nitric oxide, Non Cholinergic and Non-Adrenergic Neurotransmission

Nitric oxide (NO)

It is a gaseous molecule that easily diffuses across cell membranes and regulates some physiologic and pathophysiologic processes. These processes include cardiovascular, inflammation, immune and neuronal functions.

Synthesis of nitric oxide

It is produced in a wide variety of cells especially in neurons, skeletal muscles, endothelia cells and some immune cells. In these cells, it is produced through the activities of one of these nitric oxide (NO) synthase isoenzymes; neuronal NOS (nNOS), macrophage or inducible NOS (iNOS) and endothelial NOS (eNOS). These NO isoforms synthesize NO from amino acid L-arginine in an O_2 and NADPH dependent reaction. This reaction requires enzyme bound cofactors, including heme, tetra hydrobiopterin and flavin adenine dinucleotide. NO synthesis by neuronal NOS and endothelial NOS requires agents that increase cytosolic calcium concentrations while inducible NOS do not require calcium for the synthesis of NO

Signaling mechanisms of nitric oxide

The actions of NO occur through covalent modification of proteins. This can occur through three major effector targets

Metalloproteins: NO interacts with metals especially iron in heme. Soluble guanylyl cyclase (SGC) enzyme contains heme, which binds to NO. This interaction results in the activation of SGC and increase in intracellular cGMP. cGMP activates protein kinase C (PKG) which phosphorylates specific proteins. These actions are responsible for the vasodilatory effect of NO.

NO also has affinity for iron, which is responsible for inflammatory effect on enzyme containing iron-sulfur clusters. NO inhibits mitochondrial respiration by inhibiting cytochrome oxidase.

Thiols: Thiols are compound containing the –SH group, which reacts with thiols to form nitrosothiols. Protein contains thiols in amino acid cysteine moiety. Proteins interact with NO to form nitrosothiols, which can activate or inhibit the activities of these proteins. NO also undergoes both oxidative and reductive reactions resulting in the formation of a variety of oxides of nitrogen that can nitrosylate thiols or nitrate tyrosines.

Tyrosine nitration: NO reacts with super oxide to form peroxynitrite ($ONOO^-$) a powerful oxidant that leads to DNA damage, irreversible nitration of tyrosine and oxidation of cysteine to disulfides or to various oxides. Proteins have been found to contain nitrotyrosines, the nitration of tyrosine probably by NO could impair the functions of these proteins. Protein tryrosine nitration is often used as a marker of oxidative and nitrosative stress.

Inactivation of NO: NO can be inactivated by superoxide, therefore, scavengers of superoxide anion such as superoxide dismutase may protect NO thereby, enhancing its activities.

Inhibitors of nitric oxide synthesis

NOS inhibitors are used to inhibit the activities of NO. Most of the inhibitors are arginine analogue that bind to NO arginine-binding site. Most of the inhibitors lack selectivity, because NO isoforms have high sequence similarity. However, newer NO inhibitors with selectivity for different NO isoforms haven been developed

Nitric oxide donors

They are chemical substances that release NO or related NO species. They are used to produce smooth muscle relaxation. Studies have shown that different biologic activities depend on the type of NO released. Examples include, organic nitrites, sodium nitroprusside, hybrid NO donors, and organic nitrates. An example of organic nitrate is nitroglycerin. Nitroglycerin dilates veins and coronary arteries; it is metabolized to NO by mitochondrial aldehyde reductase. Other organic nitrate such as isosorbide denitrate are metabolized to NO-releasing species by an unidentified enzyme.

Sodium nitroprusside: It is used for the reduction of arterial hypertension. It secretes NO in response to light as well as chemical or enzymatic mechanism in cell membranes.

Hybride NO donors: This is a new strategy employed which involves the incorporation of NO-donating moieties into clinically use cardiovascular drugs. An example is the incorporation of nitrosothiol moiety in captopril (SNOCaP), which is currently been examined for its efficacy in cardiovascular disorders.

NO gas inhalation: Inhalation of NO gas has been used therapeutically. It has been used to reduce pulmonary artery pressure and improved perfusion of ventilated areas of the lung. It has been used for acute respiratory distress syndrome, acute hypoxia and cardiopulmonary resuscitation**.**

Non- cholinergic and non-adrenergic neurotransmission

The autonomic effector tissues e.g. gut, airway and bladder have motor and sensory non-cholinergic and non-adrenergic fibres. These fibres have peptides as their most common neurotransmitter. Other substances like nitric oxide synthase and purines are also present. The enteric system in the gut is an example of a system with non-cholinergic (NC) and non-adrenergic **(**NA) neurons. In addition to its cholinergic and adrenergic fibres, the small intestine has NC and NA neurons. These neurons contain one or more of the following neurotransmitters; nitro oxide synthase, substance P, calcitonin gene related peptide, cholecystokinins, dynorphin, enkephalins, neuropeptide Y and vasoactive intestinal peptide. The enteric nervous system (ENS) uses these neurotransmitters to coordinate activities with the central nervous system (CNS) and the autonomic nervous system (ANS).

Non cholinergic and non-adrenergic neurotransmitters

Endothelins: There are 3 isoforms of endothelins (ET_1, ET_2 and ET_3) which are well distributed in the body. ET_1- is produced by neurons in the CNS, sertoli, breast epithehal cells and other cells. ET_2 is predominantly produced in the kidney and gut. ET_3- is produced in the brain, kidney, lung and gastrointestinal tract. Endothelins have two sub-types of receptors (ETA and ETB). ET_1 has high affinity for ETA receptor while ET_2 and ET_3 have high affinity for ETB receptor. Endothelins produce different types of actions in the body. They cause dose dependent vasoconstriction of vascular beds and have positive inotropic and chronotropic actions on the heart. On the kidney, they cause vasoconstriction which causes decrease glomeruli filtration rate leading to decrease water and salt excretion.

Vasoactive intestinal peptides: They are well distributed in the CNS and PNS where they function as neurotransmitters and neuromodulators. They are present in the gastrointestinal tract, lung, kidney and blood vessels. They have varieties of actions, which include the production of vasodilation in vascular beds, positive inotropic and chronotropic effects on the heart.

Calcitonin- gene-related peptide: It is present in large quantity in cells of the thyroid gland and is well distributed in the CNS, PNS and gastrointestinal tract. When administered it produces a variety of effects, which include hypertension, suppression of appetite and tachycardia.

Substance P: It belongs to the tachykinin family. It is present in the CNS as a neurotransmitter and in the enteric nervous system where it acts as a local hormone. It acts through NK1, NK2 and NK3 receptors, but has more infinity for NK1 receptor. It has a variety of actions which include production of hypotension in humans due to vasodilation, contractions of intestinal and bronchial smooth muscles and the stimulation of salivary gland secretion. It also causes diuresis and natriuresis.

Neuropeptide Y: It is found in CNS and PNS. In the sympathetic NS, it is localized in adrenergic neurons where it functions as a vasoconstrictor and co-transmitter with norepinephrine. It produces a variety of CNS effects which include hypothermia, respiratory depression and hypertension. It has positive inotropic and chronotropic effects on the heart. It is a potent renal vasoconstrictor and suppresses rennin secretion.