14.4B: Adrenergic Neurons and Receptors

Adrenergic receptors are molecules that bind catecholamines. Their activation leads to overall stimulatory and sympathomimetic responses.

Learning Objectives

• Describe adrenergic neurons and receptors in the autonomic nervous system

Key Points

• Adrenergic receptors consist of two main groups, α and β, multiple subgroups (α1, α2, β1, β2, β3), and several subtypes of the α2 subgroup (α2A, α2B, α2C).
• Epinephrine binds both α and β adrenergic receptors to cause vasoconstriction and vasodilation.
• When activated, the α1 receptor triggers smooth muscle contraction in blood vessels in the skin, gastrointestinal tract, kidney, and brain, among other areas.
• When activated, the α2 receptor triggers inhibition of insulin and the induction of glucagon release in the pancreas, contraction of GI tract sphincters, and increased thrombocyte aggregation.

Key Terms

• adrenoreceptor: These are a class of G protein-coupled receptors that are targets of the catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline). Many cells possess these receptors, and
the binding of a catecholamine to the receptor will generally stimulate the sympathetic nervous system.

- **G protein-coupled receptors**: These comprise a large protein family of transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. Any adrenergic effects on cells are generally mediated by G protein-coupled receptors.

- **adrenergic receptor**: Any of several sites in the surface membranes of cells innervated by adrenergic neurons.

The adrenergic receptors (or adrenoceptors) are a class of metabotropic G protein-coupled receptors that are targets of the catecholamines, especially norepinephrine or noradrenaline, and epinephrine (adrenaline). Although dopamine is a catecholamine, its receptors are in a different category.

Many cells possess these receptors, and the binding of an agonist will generally cause a sympathetic (or sympathomimetic) response (e.g., the fight-or-flight response). For instance, the heart rate will increase, pupils will dilate, energy will be mobilized, and blood flow will be diverted from non-essential organs to skeletal muscle.

Adrenaline (epinephrine): The 2D structure of adrenaline (epinephrine) is illustrated.

Noradrenaline (norepinephrine): The 2D structure of noradrenaline (norepinephrine) is illustrated here.

There are two main groups of adrenergic receptors, α and β, with several subtypes. α receptors have the subtypes α1 (a Gq coupled receptor) and α2 (a Gi coupled receptor). Phenylephrine is a selective agonist of the α receptor.

β-receptors have the subtypes β1, β2, and β3. All three are linked to Gs proteins (although β2 also couples to Gi), which in turn are linked to adenylyl cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger cAMP. Downstream effectors of cAMP include the cAMP-dependent protein, kinase (PKA), which mediates some of the intracellular events following hormone binding. Isoprenaline is a nonselective agonist.

Adrenaline or noradrenaline are receptor ligands to α1, α2, or β-adrenergic receptors (the pathway is shown in the following diagram).

- α1 couples to Gq, which results in increased intracellular Ca2+ that results in smooth muscle contraction.
• α2, on the other hand, couples to Gi, which causes a decrease of cAMP activity, that results in smooth muscle contraction.
• β receptors couple to Gs, and increases intracellular cAMP activity, resulting in heart muscle contraction, smooth muscle relaxation, and glycogenolysis.

Adrenergic signal transduction: This schematic shows the mechanism of adrenergic receptors. Adrenaline and noradrenaline are ligands to α1, α2, or β-adrenergic receptors. α1-receptors couple to Gq, resulting in increased intracellular Ca2+ and causing smooth muscle contraction. α2 receptors couple to Gi, causing a decrease in cAMP activity and resulting in smooth muscle contraction. β-receptors couple to Gs, increasing intracellular cAMP activity and resulting in heart muscle contraction, smooth muscle relaxation, and glycogenolysis.

Adrenaline (epinephrine) reacts with both α- and β-adrenoceptors, causing vasoconstriction and vasodilation, respectively. Although α receptors are less sensitive to epinephrine, when activated, they override the vasodilation mediated by β-adrenoceptors. The result is that high levels of circulating epinephrine cause vasoconstriction. At lower levels of circulating epinephrine, β-adrenoceptor stimulation dominates, producing an overall vasodilation.

Smooth muscle behavior is variable depending on anatomical location. One important note is the differential effects of increased cAMP in smooth muscle compared to cardiac muscle. Increased cAMP will promote relaxation in smooth muscle, while promoting increased contractility and pulse rate in cardiac muscle.

α-receptors have several functions in common, but also individual effects. Common (or still unspecified) effects include: vasoconstriction of cardiac arteries (coronary artery), vasoconstriction of veins, and decreased motility of smooth muscle in the gastrointestinal tract.

α1-adrenergic receptors are members of the G protein-coupled receptor superfamily. On activation, a heterotrimeric G protein, Gq, activates phospholipase C (PLC).
The PLC cleaves phosphatidylinositol 4,5-bisphosphate (PIP2), which in turn causes an increase in inositol triphosphate (IP3) and diacylglycerol (DAG). The former interacts with calcium channels of the endoplasmic and sarcoplasmic reticulum, thus changing the calcium content in a cell. This triggers all other effects.

Specific actions of the α1-receptor mainly involve smooth muscle contraction. It causes vasoconstriction in many blood vessels, including those of the skin, gastrointestinal system, kidney (renal artery), and brain. Other areas of smooth muscle contraction are:

- Ureter.
- Vas deferens.
- Hair (arrector pili muscles).
- Uterus (when pregnant).
- Urethral sphincter.
- Bronchioles (although minor to the relaxing effect of β2 receptor on bronchioles).
- Blood vessels of ciliary body (stimulation causes mydriasis).

Further effects include glycogenolysis and gluconeogenesis from adipose tissue and the liver, as well as secretion from sweat glands, and Na+ reabsorption from kidney. Antagonists may be used in hypertension.

There are 3 highly homologous subtypes of α2 receptors: α2A, α2B, and α2C.

**α2-Receptor Effects**

- Inhibition of insulin release in the pancreas.
- Induction of glucagon release from the pancreas.
- Contraction of sphincters of the gastrointestinal tract.
- Negative feedback in the neuronal synapses—presynaptic inhibition of noradrenalin release in CNS.

**β1-Receptor Effects**

- Increases cardiac output, by raising heart rate (positive chronotropic effect), increasing impulse conduction (positive dromotropic effect), and increasing contraction (positive inotropic effect), thus increasing the volume expelled with each beat (increased ejection fraction).
- Increases renin secretion from the juxtaglomerular cells of the kidney.
- Increases ghrelin secretion from the stomach.

**β2-Receptor Effects**

- Smooths muscle relaxation, e.g., in bronchi and the GI tract (decreased motility).
- Lipolysis in adipose tissue.
- Anabolism in skeletal muscle.
• Relaxes a non-pregnant uterus.
• Dilates arteries to skeletal muscle.
• Glycogenolysis and gluconeogenesis.
• Stimulates insulin secretion.
• Contracts the sphincters of the GI tract.
• Thickens secretions from the salivary glands.
• Inhibits histamine release from mast cells.
• Increases renin secretion from the kidney.
• Relaxation of bronchioles (salbutamol, a beta-2 agonist, relieves bronchiole constriction).