→ All types of B receptors stimulate adenylyl cyclase (enzymes that are responsible for conversion of ATP to cAMP.

The main effects of receptor activation:

| Receptor | Effect |
|---|---|
| A1 | → Vasoconstriction.<br>→ Relaxation of gastrointestinal smooth muscle, salivary secretion.<br>→ Constricts blood vessels and bronchi.<br>→ Contracts most of the smooth muscle tissue. |
| A2 | → Inhibition of transmitter release (including noradrenaline and ACh release from autonomic nerves)<br>→ Platelet aggregation<br>→ Vascular smooth muscle contraction<br>→ Insulin release (rises with the increased level of blood glucose (sugar)) |
| B1 | → Increases cardiac rate and force |
| B2 | → Bronchodilation, vasodilation, relaxation of visceral smooth muscle, muscle tremor |
| B3 | → Lipolysis (break down of fats by hydrolysis and other lipids to release fatty acids) and thermogenesis (production of heat).<br>→ Bladder muscle relaxation. |

Noradrenergic transmission synthesis involves the following steps:
1. L-Tyrosine, an aromatic amino acid, is converted to dopa by tyrosine hydroxylase. Tyrosine hydroxylase occurs only in catecholaminergic neurons.
2. Dopa is converted to dopamine by another enzyme (dopa decarboxylase).
3. Dopamine is converted to noradrenaline by DBH, located in the synaptic vesicles.
4. Noradrenaline is converted to adrenaline by another enzyme (PNM).

Transmitter storage
→ Noradrenaline is stored at high concentration in synaptic vesicles, together with ATP, chromogranin and DBH, all of which are released by exocytosis. Transport of noradrenaline into vesicles occurs by a reserpine-sensitive transporter (VMAT). Endogenous and exogenous catecholamines are metabolised mainly by an intracellular enzyme – Monoamine Oxidase (MAO). This means that noradrenaline content of cytosol (an aqueous component of cytoplasm of a cell) is normally low due to MAO in nerve terminals.
→ Transmitter release occurs normally by Ca2+-mediated exocytosis from varicosities (permanently dilated veins) on the terminal network.
→ Non-exocytotic release occurs to indirectly acting drugs like amphetamine, which displace noradrenaline from vesicles. The displaced noradrenaline escapes via the Noradrenaline Transporters (NET). Transmitter action is generally terminated by reuptake of noradrenaline into nerve terminals via the NET transporters. NET is blocked by anti-depressant drugs, as well as cocaine.
Noradrenaline release is controlled by auto-inhibitory feedback, mediated by A2 receptors.

Adrenoceptor Agonists:

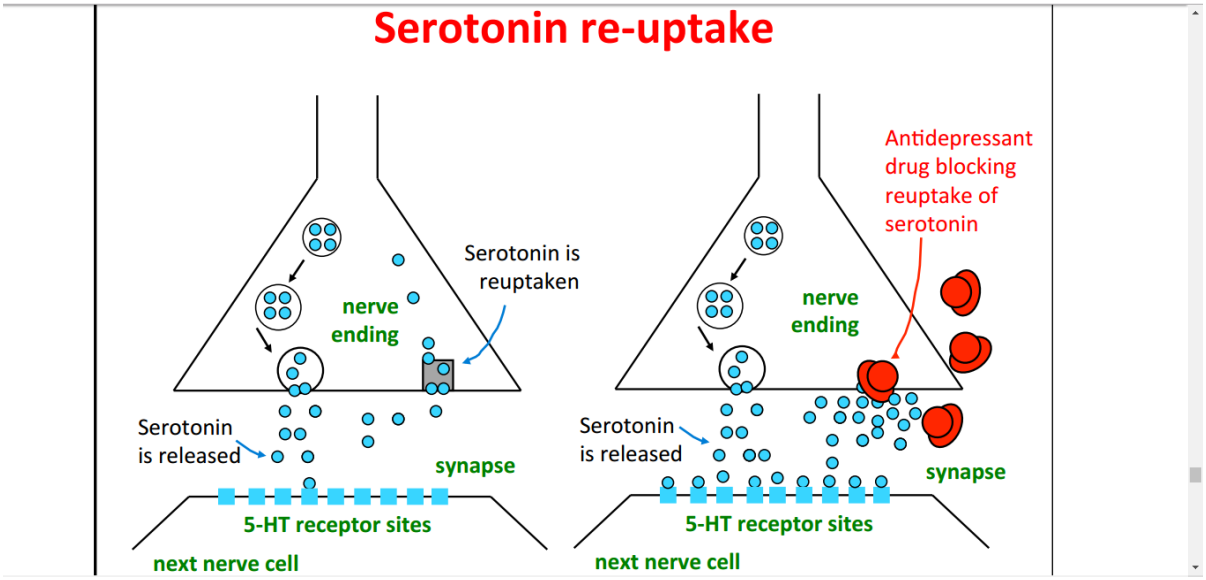
Actions:
1. Smooth Muscle
Almost all types of smooth muscle contract in response to A adrenoceptors stimulation, through intracellular Calcium release. Meanwhile, stimulation of B adrenoceptors causes relaxation of most type of smooth muscle by increasing cAMP formation.
2. Nerve Terminals
Presynaptic adrenoceptors are present on both cholinergic and noradrenergic nerve terminals. The main effect (alpha-mediated) is inhibitory.
3. Heart
Catecholamines, acting on B1 receptors, exert a powerful stimulant effect on the heart (both force and rate are increased).
4. Metabolism
Catecholamines encourage the conversion of energy stores (glycogen and fat) to freely available fuels (glucose and free fatty acids).
→ Activation of A2 receptors inhibits insulin secretion, an effect that further contributes to hyperglycaemia. The production of leptin is also inhibited.

In humans, adrenaline and other B2 agonists cause a marked tremor, the shakiness that accompanies fear, excitement or the excessive use of B2 agonists (E.g. Salbutamol – for treating asthma).
B2 receptors also cause long-term changes in the expression of sarcoplasmic reticulum proteins that control contraction kinetics, and thereby increase the rate and force of contraction of skeletal muscle (E.g. Clenbuterol – an anabolic drug).

Summery
→ Noradrenaline and Adrenaline show little receptor selectivity.
→ Selective A1 agonists include **phenylephrine (Used as a vasoconstrictor and nasal decongestant)**.
→ Selective A2 agonists include **Clonidine, causing a fall in blood pressure, partly by inhibition of noradrenaline release.**
→ All B1 receptor agonists can cause cardiac dysrhythmia.
→ Selective B2 agonists include Salbutamol, used for bronchodilator action in asthma.
→ A selective B3 agonist, Mirabegron, is used to treat overactive bladder.

| Type of Antagonist | A-Adrenoceptor antagonist | B-Adrenoceptor antagonist |
|---|---|---|
| Comments | • Used to treat hypertension (Abnormally high blood pressure). | • Important hazards are bronchoconstriction, and cardiac failure.<br>• Side effects include cold extremities (limbs of the body), insomnia, depression, and fatigue.<br>• Some show fast metabolism, hence poor bioavailability. |
| Clinical Uses | • Severe Hypertension<br>• Preparation for surgery | • Cardiovascular/ Glaucoma/ Anxiety/ Migraine |
| Unwanted Effects | | • Bronchoconstriction |

| | | |
|---|---|---|
| | | • Cardiac Depression<br>• Bradycardia (slow heart action)<br>• Fatigue<br>• Cold Extremities |




Selective serotonin re-uptake inhibitors (SSRIs)

- Like the catecholamines, serotonin has presynaptic uptake site (distinct) and is recycled.
- SSRIs (e.g. Fluoxitine (Prozac)) are in wide use as antidepressants and some psychiatric disorders.
- Other useful antidepressants include reserpine (releaser), the tricyclic antidepressants and monoamine oxidase inhibitors: all increase the levels of serotonin (as well as catecholamines) in synapses.

Serotonin and irritable bowel syndrome (IBS)

- It is a functional motility disorder, refers to recurrent abdominal pain with disturbed bowel habits.
- 9-12% affected
- The new generation of 5HT4 receptor agonists has the potential to offer superior selectivity in the treatment of constipation, IBS-C, and a variety of other motility disorders.
- Approved for use in patients with chronic functional constipation in Europe, Canada, and Australia.

Clinical uses of serotonin agents

| Receptor name | Drug name | Treatment for |
|---|---|---|
| 5HT(1A) agonist | Buspirone | Anxiety, depression |
| 5HT(1D) agonist | Sumatriptan | Migraine |

| | | |
|---|---|---|
| 5HT2 antagonist | Methysergide | Migraine (prophylactically) |
| 5HT3 antagonist | Ondansteron | Chemotherapy induced emesis |
| 5HT4 | Prucalopride (new) | Constipation |
| Uptake Inhibitor | Fluoxitine (Prozac) | Depression, OCD |