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**Noradrenergic transmission**

Catecholamines are compounds containing a catechol moiety the most important are:

* **Noradrenaline** (**norepinephrine**), a transmitter released by sympathetic nerve terminals.
* **Adrenaline** (**epinephrine**), a hormone secreted by the adrenal medulla.
* **Dopamine**, the metabolic precursor of noradrenaline and adrenaline, also a transmitter/neuromodulator in the central nervous system.
* **Isoprenaline** (also known as **isoproterenol**), a synthetic derivative of noradrenaline

**CLASSIFICATION OF ADRENOCEPTORS:**

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| * Main pharmacological classification into α and β subtypes * Adrenoceptor subtypes:   + two main α-adrenoceptor subtypes, α1 and α2, each divided into three further subtypes   + three β-adrenoceptor subtypes (β1, β2, β3) * Second messengers:   + α1 receptors activate phospholipase C   + α2 receptors inhibit adenylyl cyclase, decreasing cAMP formation   + All types of β receptor stimulate adenylyl cyclase. * The main effects of receptor activation are as follows:   + α1 receptors: vasoconstriction, relaxation of gastrointestinal smooth muscle, salivary secretion and hepatic glycogenolysis   + α2 receptors: inhibition of transmitter release (including noradrenaline and acetylcholine release from autonomic nerves), platelet aggregation, contraction of vascular smooth muscle, inhibition of insulin release and increase growth hormone release   + β1 receptors: increased cardiac rate and force, delayed cardiac hypertrophy   + β2 receptors: bronchodilatation, vasodilatation, relaxation of visceral smooth muscle, hepatic glycogenolysis and muscle tremor   + β3 receptors: lipolysis. |

Noradrenergic neurons in the periphery are postganglionic sympathetic neurons whose cell bodies lie in sympathetic ganglia. They generally have long axons that end in a series of varicosities strung along the branching terminal network. These varicosities contain numerous synaptic vesicles, which are the sites of synthesis and release of noradrenaline and of co-released mediators such as ATP and neuropeptide Y.

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**Biosynthesis of catecholamine**

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| The metabolic precursor for noradrenaline is l-tyrosine, Tyrosine hydroxylase, a cytosolic enzyme that catalyses the conversion of tyrosine to dihydroxyphenylalanine (dopa), is found only in catecholamine-containing cells. . This first hydroxylation step is the main control point for noradrenaline synthesis.   |  | | --- | | The tyrosine analogue α-methyltyrosine strongly inhibits tyrosine hydroxylase and may be used to block noradrenaline synthesis. |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Then, conversion of dopa to dopamine, by dopa decarboxylase, a cytosolic enzyme no confined to catecholamine-synthesising cells. Dopa decarboxylase activity is not rate limiting for noradrenaline synthesis.   |  | | --- | |  |  |  | | --- | | Many drugs inhibit DBH, including copper-chelating agents and disulfiram .Such drugs can cause a partial depletion of noradrenaline stores and interference with sympathetic transmission. |  |  | | --- | | Phenylethanolamine N-methyl transferase (PNMT) catalyses the N-methylation of noradrenaline to adrenaline. |  |  |  |  | | --- | --- | --- | | |  | | --- | | Most of the noradrenaline in nerve terminals or chromaffin cells is contained in vesicles; only a little is free in the cytoplasm under normal circumstances. The concentration in the vesicles is very high and is maintained by the vesicular monoamine transporter (VMAT Certain drugs, such as reserpine block this transport and cause nerve terminals to become depleted of their vesicular noradrenaline stores. The vesicles contain two major constituents besides noradrenaline, namely ATP and chromogranin A. |  |  | | --- | |  | | | | |
| Noradrenergic transmission |

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**DRUGS ACTING ON NORADRENERGIC TRANSMISSION**

* **ADRENOCEPTOR AGONISTS**

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| All types of smooth muscle, except that of the gastrointestinal tract, contract in response to stimulation of α1-adrenoceptors, through activation of the signal transduction mechanism. |

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| The α receptors involved in smooth muscle contraction are mainly α1 in type, although vascular smooth muscle possesses both α1 and α2 receptors. It appears that α1 receptors lie close to the sites of release (and are mainly responsible for neurally mediated vasoconstriction), while α2 receptors lie elsewhere on the muscle fibre surface and are activated by circulating catecholamines. |

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| Stimulation of β receptors causes relaxation of most kinds of smooth muscle by increasing cAMP formation and reduces intracellular Ca2+ concentration. |

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| Relaxation is usually produced by β2 receptors, although the receptor that is responsible for this effect in gastrointestinal smooth muscle is not clearly β1 or β2. In the vascular system, β2-mediated vasodilatation is (particularly in humans) mainly endothelium dependent and mediated by nitric oxide release . |

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| The powerful inhibitory effect of the sympathetic system on gastrointestinal smooth muscle is produced by both α and β receptors due to stimulation of presynaptic α2 receptors which inhibit the release of excitatory transmitters (e.g. acetylcholine) from intramural nerves. |

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| Bronchial smooth muscle is relaxed by activation of β2-adrenoceptors, and selective β2 agonists are important in the treatment of asthma. Uterine smooth muscle responds similarly, and these drugs are also used to delay premature labour . |

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| α1-Adrenoceptors also mediate a long-lasting trophic response, stimulating smooth muscle proliferation in various tissues, for example in blood vessels and in the prostate gland, which is of pathological importance. *Benign prostatic hyperplasia* is commonly treated with α-adrenoceptor antagonists . |

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| Presynaptic adrenoceptors are present on both cholinergic and noradrenergic nerve terminals . The main effect (α2 mediated) is inhibitory. |

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| |  | | --- | | Heart Catecholamines, acting on β1 receptors, exert a powerful stimulant effect on the heart .Both the heart rate (*chronotropic effect*) and the force of contraction (*inotropic effect*) are increased. |  |  | | --- | | Cardiac hypertrophy occurs in response to activation of both β1 and α1 receptors, probably by a mechanism similar to the hypertrophy of vascular and prostatic smooth muscle. This may be important in the pathophysiology of hypertension and cardiac failure, conditions associated with sympathetic overactivity . | | Activation of α2 receptors inhibits insulin secretion. The production of *leptin* by adipose tissue is also inhibited. Adrenaline-induced hyperglycaemia in humans is blocked completely by a combination of α and β antagonists but not by either on its own. Selective β3-receptor agonists (e.g. BRL 37344) have been developed as possible treatments for obesity.   |  | | --- | | Adrenaline and other β2 agonists cause a marked tremor, the shakiness that accompanies fear, excitement or the excessive use of β2 agonists (e.g. **salbutamol**) in the treatment of asthma being examples of this. |  |  |  | | --- | --- | | Histamine release is inhibited by catecholamines, acting on β2 receptors.   |  | | --- | | Lymphocytes and other cells of the immune system also express adrenoceptors (mainly β-adrenoceptors). Lymphocyte proliferation, lymphocyte-mediated cell killing, and production of many cytokines are inhibited by β-adrenoceptor agonists. | | | | |
| **Adrenoceptor agonists:** |

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| * **Noradrenaline** and **adrenaline** show relatively little receptor selectivity. * Selective α1 agonists include **phenylephrine** and **oxymetazoline**. * Selective α2 agonists include **clonidine** and **α-methylnoradrenaline**. They cause a fall in blood pressure, partly by inhibition of noradrenaline release and partly by a central action. Methylnoradrenaline is formed as a false transmitter from **methyldopa**, developed as a hypotensive drug * Selective β1 agonists include **dobutamine**. Increased cardiac contractility may be useful clinically, but all β1 agonists can cause cardiac dysrhythmias. * Selective β2 agonists include **salbutamol**, **terbutaline** and **salmeterol**, used mainly for their bronchodilator action in asthma. * Selective β3 agonists may be developed for the treatment of obesity. |

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| **Clinical uses of adrenoceptor agonists** |

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| * Cardiovascular system:   + cardiac arrest: **adrenaline**   + cardiogenic shock ; **dobutamine** (β1 agonist). * Anaphylaxis: adrenaline. * Respiratory system:   + asthma : selective β2-receptor agonists (**salbutamol**, **terbutaline**, **salmeterol**, **formoterol**)   + Nasal decongestion: drops containing **xylometazoline** or **ephedrine** for short-term use. * Miscellaneous indications:   + **Adrenaline**: with local anaesthetics to prolong their action. * premature labour **salbutamol**; ritodrine and isoxuprine   + α2 agonists (e.g. **clonidine**): to lower blood pressure and intraocular pressure; as an adjunct during drug withdrawal in addicts to reduce menopausal flushing; and to reduce frequency of migraine attacks ,dwarfism   + clenobuterol has anabolic effects |

**ADRENOCEPTOR ANTAGONISTS**

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| **α-Adrenoceptor antagonists** |

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| * non-selective between subtypes (e.g. **phenoxybenzamine**, **phentolamine**) * α1 selective (e.g. **prazosin**, **doxazosin**, **terazosin**) * α2 selective (e.g. **yohimbine**, **idazoxan**) |

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| **1-Phenoxybenzamine** is not specific for α receptors, and also antagonises the actions of acetylcholine, histamine and 5-HT. It is long lasting because it binds covalently to the receptor.  2-**Phentolamine** is more selective, but it binds reversibly and its action is short lasting. In humans, these drugs cause a fall in arterial pressure (because of block of α-receptor-mediated vasoconstriction) and postural hypotension. The cardiac output and heart rate are increased. This is a reflex response to the fall in arterial pressure, mediated through β receptors. The concomitant block of α2 receptors tends to increase noradrenaline release, which has the effect of enhancing the reflex tachycardia that occurs with any blood pressure-lowering agent.. |

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| **3-Labetalol** and **carvedilol** are mixed α1- and β-receptor-blocking drugs, although clinically they act predominantly on β receptors. Carvedilol is used mainly to treat hypertension and heart failure labetalol is used to treat hypertension in pregnancy. |

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| **4-Prazosin** was the first α1-selective antagonist. Similar drugs with longer half-lives (e.g. **doxazosin**, **terazosin**), They are highly selective for α1-adrenoceptors and cause vasodilatation and fall in arterial pressure, but less tachycardia than occurs with non-selective α-receptor antagonists, presumably because they do not increase noradrenaline release from sympathetic nerve terminals. Some postural hypotension may occur. |

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| The α1-receptor antagonists cause relaxation of the smooth muscle of the bladder neck and prostate capsule, and inhibit hypertrophy of these tissues, and are therefore useful in treating urinary retention associated with *benign prostatic hypertrophy*.  **5-Tamsulosin**, α1A-receptor antagonist, shows some selectivity for the bladder, and causes less hypotension than drugs such as prazosin, which act on α1B receptors to control vascular tone. |

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| It is believed that α1A receptors play a part in the pathological hypertrophy not only of prostatic and vascular smooth muscle, but also in the cardiac hypertrophy that occurs in hypertension and heart failure. |

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| **6-Yohimbine** and **idazoxan**. as an aphrodisiac.   |  | | --- | |  |  |  | | --- | | *Phaeochromocytoma* is a catecholamine-secreting tumour of chromaffin tissue, which causes episodes of severe hypertension. A combination of α- and β-receptor antagonists is the most effective way of controlling the blood pressure. | |

**β-Adrenoceptor antagonists**

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| They were first discovered in 1958the first compound, **dichloroisoprenaline**, Further development led to **propranolol**, which is much more potent and a pure antagonist that blocks β1 and β2 receptors equally. The potential clinical advantages of drugs with some partial agonist activity, and/or with selectivity for β1 receptors, led to the development of **practolol** (selective for β1 receptors but withdrawn because of its toxicity), **oxprenolol** and **alprenolol** (non-selective with considerable partial agonist activity), and **atenolol** (β1 selective with no agonist activity). Two newer drugs are **carvedilol** (a non-selective β-adrenoceptor antagonist with additional α1-blocking activity) and **nebivolol** (a β1-selective antagonist that also causes vasodilatation by inducing endothelial nitric oxide production. Both of these drugs have proven more effective than conventional β-adrenoceptor antagonists in treating heart failure. Most β-receptor antagonists are inactive on β3 receptors so do not affect lipolysis. |

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| In a subject at rest, propranolol causes little change in heart rate, cardiac output or arterial pressure, but reduces the effect of exercise or excitement on these variables .Drugs with partial agonist activity, such as oxprenolol, increase the heart rate at rest but reduce it during exercise. Maximum exercise tolerance is considerably reduced in normal subjects, partly because of the limitation of the cardiac response, and partly because the β-mediated vasodilatation in skeletal muscle is reduced. Coronary flow is reduced, but relatively less than the myocardial oxygen consumption, so oxygenation of the myocardium is improved, an effect of importance in the treatment of angina pectoris In normal subjects, the reduction of the force of contraction of the heart is of no importance, but it may have serious consequences for patients with heart disease. |

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| Patients with hypertension (although not normotensive subjects) show a gradual fall in arterial pressure that takes several days to develop fully. The mechanism is complex and involves the following:   * reduction in cardiac output * reduction of renin release from the juxtaglomerular cells of the kidney * A central action, reducing sympathetic activity. * Inhibition of excitatory presynaptic ß-receptor   Carvedilol and nebivolol are particularly effective in lowering blood pressure, because of their additional vasodilator properties. |

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| Blockade of the facilitatory effect of presynaptic β receptors on noradrenaline release may also contribute to the antihypertensive effect. Because reflex vasoconstriction is preserved, postural and exercise-induced hypotension are less than with many other antihypertensive drugs. |

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| |  | | --- | | Airways resistance in normal subjects is only slightly increased by β-receptor antagonists, and this is of no consequence. In asthmatic subjects, however, non-selective β-receptor antagonists can cause severe bronchoconstriction, |  |  | | --- | | In diabetic patients, the use of β-receptor antagonists increases the likelihood of exercise-induced hypoglycaemia, because the normal adrenaline-induced release of glucose from the liver is diminished. |  |  | | --- | |  |  |  | | --- | |  |  |  | | --- | |  |  |  |  |  | | --- | --- | --- | | Paradoxically, β-receptor antagonists in low doses to treat cardiac failure, via inhibition of central sympathetic outflow, direct vasodilator effects and prevention of cardiac hypertrophy by interference with signalling pathways other than the major cAMP pathway-a phenomenon   |  | | --- | |  |  |  | | --- | |  | | | |
| **Clinical uses of β-adrenoceptor antagonists:** |

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| * Cardiovascular.   + angina pectoris   + myocardial infarction   + dysrhythmias   + heart failure   + hypertension . * Other uses:   + glaucoma (e.g. **timolol** eye drops)   + thyrotoxicosis . as adjunct to definitive treatment (e.g. preoperatively)   + anxiety : to control somatic symptoms (e.g. palpitations, tremor)   + Migraine prophylaxis .   + Benign essential tremor  |  | | --- | | **Unwanted effects** |  |  | | --- | |  |  |  | | --- | | * Bronchoconstriction |  |  | | --- | |  |  |  | | --- | | * Cardiac depression |  |  | | --- | |  |  |  | | --- | | * Bradycardia |  |  | | --- | |  |  |  | | --- | | * Hypoglycemia |  |  | | --- | |  |  |  | | --- | | * Fatigue |  |  | | --- | |  |  |  | | --- | | * Cold extremities |  |  | | --- | |  |  |  | | --- | | * Bad dreams (nightmare), which occur mainly with highly lipid-soluble drugs such as propranolol, which enter the brain easily. |  |  | | --- | |  | |  |   Several drugs that act on adrenoceptors have the characteristics of partial agonists, i.e. they block receptors and thus antagonise the actions of full agonists, but also have a weak agonist effect of their own. Some β-adrenoceptor-blocking drugs (e.g. **alprenolol**, **oxprenolol**) cause, under resting conditions, an increase in heart rate while at the same time opposing the tachycardia produced by sympathetic stimulation. Though in normal hearts cardiac stimulation is mediated through β1 receptors, in heart failure β2 receptors contribute significantly.  There is evidence that β-adrenoceptor agonists and partial agonists may act not only through cAMP formation, but also through other signal transduction pathways (e.g. the mitogen-activated protein [MAP] kinase pathway and that the relative contribution of these signals differs for different drugs.   |  | | --- | | **DRUGS THAT AFFECT NORADRENALINE SYNTHESIS :** |  |  | | --- | | 1-**α-methyltyrosine**, which inhibits tyrosine hydroxylase (used rarely to treat phaeochromocytoma), and **carbidopa**, a hydrazine derivative of dopa, which inhibits dopa decarboxylase and is used in the treatment of parkinsonism. |  |  | | --- | | **2-Methyldopa**, converted to the false transmitter α-methylnoradrenaline. it is more active on presynaptic (α2) receptors, so the autoinhibitory feedback mechanism operates more strongly than normal, thus reducing transmitter release below the normal levels. |  |  | | --- | | **3-Hydroxydopamine** : is a neurotoxin is taken up selectively by noradrenergic nerve terminals, where it is converted to a reactive quinone, which destroys the nerve terminal, producing a 'chemical sympathectomy'.  **4-MPTP (1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine**;) is a similar selective neurotoxin. |  |  | | --- | | **5-Droxidopa** converted to noradrenaline directly by dopa decarboxylase, bypassing the DBH-catalysed hydroxylation step, which is normally rate limiting. It raises blood pressure by increasing noradrenaline release. |  |  | | --- | | **DRUGS THAT AFFECT NORADRENALINE STORAGE** |  |  | | --- | | Reserpine, at very low concentration, blocks the transport of noradrenaline and other amines into synaptic vesicles, by blocking the vesicular monoamine transporter. Noradrenaline accumulates instead in the cytoplasm, where it is degraded by MAO. |  |  | | --- | | **DRUGS THAT AFFECT NORADRENALINE RELEASE** |  |  | | --- | | Drugs can affect noradrenaline release in four main ways:   1. By directly blocking release (noradrenergic neuron-blocking drugs). 2. By evoking noradrenaline release in the absence of nerve terminal depolarisation (indirectly acting sympathomimetic drugs). 3. By acting on presynaptic receptors that indirectly inhibit or enhance depolarisation-evoked release. Examples angiotensin II, dopamine and prostaglandins. 4. By increasing or decreasing available stores of noradrenaline . |  |  | | --- | | **NORADRENERGIC NEURON-BLOCKING DRUGS** |  |  | | --- | |  | |  | |  |  |  | | --- | | **guanethidine** The main effect of guanethidine is to inhibit the release of noradrenaline from sympathetic nerve terminals. It has little effect on the adrenal medulla, and none on nerve terminals that release transmitters other than noradrenaline. Drugs very similar to it include **bretylium**, **bethanidine** and **debrisoquin** |  |  | | --- | |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | |  | | --- | | **INDIRECTLY ACTING SYMPATHOMIMETIC AMINES** |  |  | | --- | |  |  |  | | --- | | The most important drugs in the indirectly acting sympathomimetic amine category are **tyramine**, **amphetamine** and **ephedrine**, which are structurally related to noradrenaline. Drugs that act similarly and are used for their central effects include **methylphenidate** and **atomoxetine**. |  |  |  |  | | --- | --- | --- | | These drugs have only weak actions on adrenoceptors,enhancing the effect of the released noradrenaline) and partly by inhibiting MAO.   |  | | --- | |  |  |  | | --- | | amphetamine, have important effects on the central nervous system that depend on their ability to release not only noradrenaline, but also 5-HT and dopamine from nerve terminals in the brain. Repeated doses of amphetamine cause a depletion of store of noradrenaline. The peripheral actions of the indirectly acting sympathomimetic amines include bronchodilatation, raised arterial pressure, peripheral vasoconstriction, increased heart rate and force of myocardial contraction, and inhibition of gut motility. | | | |

**INHIBITORS OF NORADRENALINE UPTAKE:**

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| 1. Tricyclic antidepressants for example **imipramine**. 2. **Cocaine**, known mainly for its abuse liability and local anaesthetic activity enhances sympathetic transmission, causing tachycardia and increased arterial pressure. Its central effects of euphoria and excitement are probably a manifestation of the same mechanism acting in the brain. |

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| The extraneuronal monoamine transporter EMT, which is important in clearing circulating adrenaline from the bloodstream, is not affected by most of the drugs that block NET. It is inhibited by **phenoxybenzamine**, and by corticosteroids . |

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**Dysautonomia (or autonomic dysfunction):** malfunction of the [autonomic nervous system](http://en.wikipedia.org/wiki/Autonomic_nervous_system) (ANS). The autonomic nervous system controls a number of functions in the body, such as [heart rate](http://en.wikipedia.org/wiki/Heart_rate), [blood pressure](http://en.wikipedia.org/wiki/Blood_pressure), [digestive tract](http://en.wikipedia.org/wiki/Digestive_tract) [peristalsis](http://en.wikipedia.org/wiki/Peristalsis), sweating, amongst others.

Signs and symptoms

* Excessive fatigue
* Excessive thirst ([polydipsia](http://en.wikipedia.org/wiki/Polydipsia" \o "Polydipsia))
* Lightheadedness, dizziness or [vertigo](http://en.wikipedia.org/wiki/Vertigo_(medical))
* Feelings of anxiety or panic (not mentally induced
* [Rapid heart rate](http://en.wikipedia.org/wiki/Tachycardia) or [slow heart rate](http://en.wikipedia.org/wiki/Bradycardia)
* [Orthostatic hypotension](http://en.wikipedia.org/wiki/Orthostatic_hypotension), sometimes resulting in [syncope](http://en.wikipedia.org/wiki/Syncope_(medicine))  (fainting)

Causes

## Management

Drugs such as [fludrocortisone](http://en.wikipedia.org/wiki/Fludrocortisone" \o "Fludrocortisone), [midodrine](http://en.wikipedia.org/wiki/Midodrine" \o "Midodrine), [ephedrine](http://en.wikipedia.org/wiki/Ephedrine) and [SSRIs](http://en.wikipedia.org/wiki/Selective_serotonin_reuptake_inhibitor) can also be used to treat symptoms. Treating dysautonomia can be difficult and usually requires a combination of drug therapies.