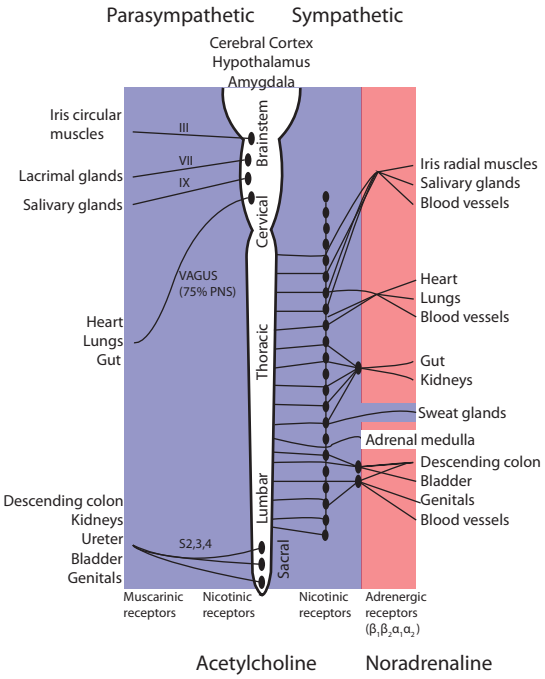
AUTONOMIC NERVOUS SYSTEM AND SYMPATHETIC DIVISION PHARMACOLOGY

Autonomic Nervous System is a division of the nervous system separate from the somatic system which maintains body homeostasis by integrating signals from afferent somatic and visceral sensors to modulate organ perfusion and function. These signals are integrated in medulla and modulated by the central autonomic network which consists (in addition to the medulla) of the cerebral cortex, hypothalamus and amygdalla. Information is then sent from the medulla to the effector organs by the efferent components of the ANS which are the parasympathetic and sympathetic nervous systems. Their tonic activity maintains cardiac activity and visceral and vascular smooth muscle in a state of immediate function from which rapid increases or decreases in autonomic outflow can adjust blood flow and organ activity in response to the environment.

Neurotransmitters of the ANS Acetylcholine is the principle transmitter released by preganglionic fibres of both the sympathetic and parasympathetic nervous systems (shown in blue on the adjacent diagram). The parasympathetic postganglionic fibres secrete acetlycholine onto their target organs, while noradrenaline is principally secreted by the postganglionic sympathetic fibres (red). The two exceptions to this are the adrenal medulla which acts as a postganglonic fibre itself and secretes 80% adrenaline and 20% noradrenaline into the systemic circulation, and sweat glands whose sympathetic postganglionic fibres secrete ACh. See also AI on neurotransmitters, and iontropes.

Receptors of the ANS Nicotinic receptors are ligand gated ion channels which are located in skeletal muscle, on postganglionic neurons in both the SNS and PNS, on adrenal chromaffin cells and within the CNS. Muscarinic receptors are seven transmembrane domain proteins coupled to a family of G Proteins that inhibit adenylyl cyclase activity. They are located on the heart where they are inhibitory, and in the smooth muscle and the glands where there are excitatory.

Like the muscarinic receptors, adrenergic receptors are also seven transmembrane domain protiens coupled to G Protiens however there are multiple subtypes and actions. There are four major subtypes $\alpha_1\alpha_2\beta_1$ and β_2. Adrenoceptors respond to catecholamines in an order of potency; for alpha adrenoceptors this is noradrenaline ≥ adrenaline ≥ isoproterenol, for beta adrenoceptors it is the reverse isoproterenol ≥ adrenaline ≥ noradrenaline. (this makes sense when you remember that we give adrenaline for bronchoconstriction not norad). There is also desensitisation in minutes from continued exposure to catecholamines and downregulation in hours.



Sympathetic nervous system pharmacology (see neuropharmacology 2 for pharmacology related to the parasympathetic division of the ANS)

The alpha adrenoceptors exist at both presynaptic and postsynaptic neuroeffector junction sites throughout the human body and are involved in cardiovascular regulation, metabolism, consciousness and nociception. Whilst there are at least six subtypes it is the alpha 1&2 subtypes which are the most important physiologically. It is possible to classify the differences in the two primary alpha receptors as shown below.

	Alpha 1 Adrenoceptors	Alpha 2 Adrenoceptors
Stimulated by	Phenylephrine, Methoxamine	Clonidine, Dexmedetomidine
Blocked by	Prazosin	Yohimbine
Order of Potency	norad≥adrenaline≥isoproterenol norad has greater potency vrs α_2	norad≥adrenaline≥isoproterenol norad has lesser potency vrs α_1
G Protien Subtypes	activates G_q stimulates phospholipase C hydrolysis and increases intracellular Ca^{2+} levels	activates G_i and results in decreased adenylyl cyclase activation of cAMP
Physiological Effects	Vasoconstriction, relaxation of GIT smooth muscle, contraction of genitourinary smooth muscles	Inhibition of noradrenaline release from nerve endings, platelet aggregation, vascular smooth muscle contraction

The beta adrenoceptors b Receptors regulate numerous functional responses, including heart rate and contractility, smooth muscle relaxation, and multiple metabolic events. All three of the b receptor subtypes (b1, b2, and b3) couple to Gs and activate adenylyl cyclase. Thus, stimulation of b adrenergic receptors leads to the accumulation of cyclic AMP, activation of PKA, and altered function of numerous cellular proteins as a result of their phosphorylation. In addition, Gs can enhance directly the activation of voltage-sensitive Ca2+ channels in the plasma membrane of skeletal and cardiac muscle.

	Beta 1 Adrenoceptors	Beta 2 Adrenoceptors
Stimulated by	No selective agonist	Salbutamol
Blocked by	Esmolol, Metoprolol, Bisoprolol	No selective antagonist but several non selective inc propanolol
Order of Potency	isoproterenol≥adrenaline≥norad	isoproterenol≥adrenaline≥norad
G Protien Subtypes	activates G_s increases cAMP through adenylyl cyclase activation	activates G_s increases cAMP through adenylyl cyclase activation
Physiological Effects	Located at the SA and AV nodes and ventricular tissue, it increases inotropy and chronotropy	Widespread distribution, located in bronchial and vascular smooth muscle, where they mediate vasodilation and bronchial relaxation

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