Histamine is a low-molecular weight, naturally occurring hydrophilic endogenous amine (autocoid) that produces a variety of physiologic and pathologic responses in different tissues and cells through G protein-coupled membrane receptors. Histamine is also an important chemical mediator of inflammation in allergic disease. Mast cells located in the skin, lungs, and gastrointestinal tract, as well as circulating basophils contain large amounts of histamine. Histamine does not easily cross the blood-brain barrier, and central nervous system (CNS) effects are usually not evident. It is formed from histidine by decarboxylase. The three known types of histamine receptors—H1, H2, and H3—are all found in both peripheral tissues and the brain. Most, if not all, of the H3 receptors are presynaptic, and they mediate inhibition of the release of histamine and other transmitters via a G protein. H1 receptors activate phospholipase C, and H2 receptors increase the intracellular cAMP concentration. The main actions in humans are; stimulation of gastric acid secretion (H2), contraction of smooth muscle other than that of blood vessels (H1), cardiac stimulation (H2), vasodilation (H1), and increased vascular permiability (H1).

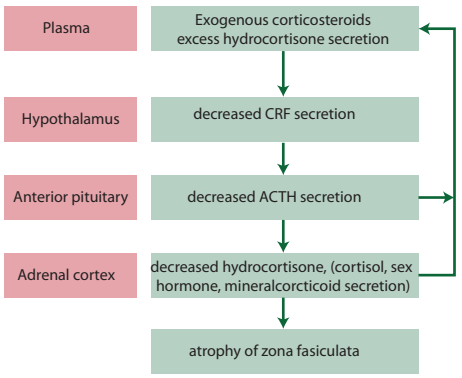
Serotonin (5-hydroxytryptamine, 5-HT) is a widely distributed endogenous vasoactive substance that evokes complex changes in the cardiovascular system (cerebral, coronary, and pulmonary vascular vasoconstriction) and functions as an important neurotransmitter in emesis and pain transmission. About 90% of the body's stores of serotonin are present in the enterochromaffin cells of the gastrointestinal tract. It is also found within the brain stem in the midline raphé nuclei which project to portions of the hypothalamus, the limbic system, the neocortex, the cerebellum, and the spinal cord. Serotonin is synthesized in cells from the amino acid precursor tryptophan, which is derived from dietary sources. The number of cloned and characterized serotonin receptors has increased rapidly. There are at least seven types of 5-HT receptors. Most of these are G protein-coupled receptors and affect adenylyl cyclase or phospholipase C. However, the 5-HT3 receptors, like nicotinic cholinergic receptors, are ligand-gated ion channels. Some of the serotonin receptors are presynaptic, and others are postsynaptic. 5-HT2A receptors mediate platelet aggregation and smooth muscle contraction. 5-HT3 receptors are present in the gastrointestinal tract and the area postrema and are related to vomiting. 5-HT4 receptors are also present in the gastrointestinal tract, where they facilitate secretion and peristalsis, and in the brain. 5-HT6 and 5-HT7 receptors in the brain are distributed throughout the limbic system, and the 5-HT6 receptors have a high affinity for antidepressant drugs.

Vasoactive intestinal peptide also known as VIP is a peptide hormone containing 29 amino acid residues that is produced in many tissues of vertebrates including the gut, pancreas (in D1 cells) and suprachiasmatic nuclei of the hypothalamus in the brain. VIP stimulates contractility in the heart, increases heart rate, causes vasodilation, increases glycogenolysis, lowers arterial blood pressure and relaxes the smooth muscle of trachea, stomach and gall bladder. In humans, the vasoactive intestinal peptide is encoded by the VIP gene. VIP has a half-life (T1/2) in the blood of about two minutes.

Insulin and the oral hypoglycaemic agents

USE & PHARMACEUTICAL	PHARMACODYNAMICS	PHARMACOKINETICS	VARIABILITY / SIDE-EFFECTS
Insulin is a naturally occuring small protien consisting of two chains (an A and B) joined by disulphide bonds with a C peptide in between. It is usually produced using recombinant DNA techniques and e.coli. Preparations are classified as short, intermediate and long duration. It should be stored at 4 degrees before being brought up to room temp before use.	Insulin binds the alpha subunit of the insulin receptor, which is then internalised second message and results in multiple effects, including translocation of glucose transporters (esp GLUT 4) to the cell membrane (increasing glucose uptake); increased glycogen formation; effects on protein synthesis, lipolysis, and lipogenesis; and activation of transcription factors that enhance DNA synthesis and cell growth and division.	Insulin is given parenterally either by IV infusion or SC injection. Its bioavailability when given subcut is 55-75%. The normal doses are in international units and are dependent on carbohydrate load and plasma glucose. The onset and duration of action varies according to the preparation. It has a small volume of distribution of 0.3 L/kg. Insulin half life is 4-6minutes, it is degraded in the liver and kidney and excreted renally.	When calorie intake is insufficient hypoglycaemia will ensue. All insulins are immunogenic but this is not often an issue. Localised lipodystrophy may occur at injection sites. SC absorption may be variable depending on local blood flow.
Sulphonylureas are separated into first generation and second generation. The second gerneration are generally used more in Australia, the most common agent is **gliclazide**. They are used to treat type II diabetes. They are also know as insulin secretagogues	In general these drugs work at the pancreas by displacing insulin from β-cells in the islets of Langerhans. For this reason they are ineffective in insulin-dependent diabetics who have no functioning β-cells. They may also induce β-cell hyperplasia, while reducing both glucagon secretion and hepatic insulinase activity.During long term administration they also reduce peripheral resistance to insulin.	Available as either an immediate release or a sustained release. Gliclazide is PO only and has very high bioavailability 97%, with peak action of the IR dose in 4-6hrs. They are extensively bound to protien (albumin). It is extensively metabolised in the liver via CYP450 mechanisms and excreted via the urine as inactive metabolites. The half life is around 10 hours.	As they increase the seceretion of insulin they may precipitate hypoglycaemia and as such should be used with caution in at risk populations such as those with heart disease and the elderly. Other side effects include nausea and rashes.
Biguanides consist primarily of the agent **metformin**. They are used in the treatment of type II diabetes.	This is thought to include delayed uptake of glucose from the gut, increased peripheral insulin sensitivity (increasing peripheral glucose utilization) and inhibition of hepatic and renal gluconeogenesis	Metformin is slowly absorbed from the gut with a bioavailability of 60%. It's onset of action is in several hours and will last for days. It is minimally bound and has a huge volume of distribution due to sequestration in the erythrocytes. There is minimal protien binding. The drug is not metabolised in the liver and is excreted in the urine unchanged, it has a plasma half life of 6-9 hours.	It may cause diarrhoea and nausea. It will cause muscle cramping and pain in up to 1 in 10 patients. It has been associated with severe lactic acidosis especially if taken by alcohol abusers or in the presence of renal impairment. It also lowers plasma cholesterol, triglycerides and low-density lipoproteins.
Glitazones are also known as the thiazolidinedi-ones. Thiazolidinediones have been primarily used in the treatment of Type II diabetes. They may be used alone or combined with other oral hypoglycaemic agents, such as the sulphonylureas or metformin. They do not cause hypoglycaemia when used in isolation. **Rosiglitazone** is a common agent in this class.	The thiazolidinediones decrease blood glucose by reducing the resistance of peripheral tissues to insulin. Consequently, they increase insulin sensitivity, reduce glycogenolysis and impair hepatic glucose release.	Rosiglitazone is given orally and has a very high bioavailability approaching 100%. It has a delayed onset of action taking weeks for the insulin sensitivity to increase peripherally to the maximim response. It is extensively protien bound (up to 99%) and almost completely metabolised in the the liver by CYP450 mechanisms. It is excreted in the urine as inactive metabolites and the half life is around 3-4 hours.	They can cause fluid retention and should not be given to patients with heart failure.

The secretion of adrenocorticotropic hormone (ACTH, also called corticotropin) and, therefore, of cortisol, is regulated by hormonal interactions among the hypothalamus, pituitary, and adrenal glands and by neural and other stimuli. ACTH is synthesized as part of a large precursor (241 amino acids in humans) called proopiomelanocortin (POMC). POMC also contains the sequences for other hormonal peptides, including the lipotropins (LPHs), melanocyte-stimulating hormones (MSHs), and beta-endorphin (beta-END). It is stimulated to be released from the anterior pituitary by the hypothalamus which senses changes in primarily in cortisol levels and the glucocorticoids. The released ACTH then travels via the blood to the adrenal cortex and increases the secretion of cortisol, hydrocortisone and the other steroid hormones. It has a short half life of 15 minutes.



Pharmacology of thyroid hormones and anti thyroid drugs (Level 2)

Pharmacology of glucocorticoids and mineralcorticoids. (Level 2)

Understand the pharmacology of glucagon (Level 3)

Christopher Andersen 2012