A great deal of research is now being carried out on newly discovered signalling systems such as the adhesion molecules and similar signalling molecules expressed on the surface of cells. The reason for this is that many of these signalling molecules are thought to be important in the cell signalling associated with the immune system. When they do not work properly they are involved in the development of arthritis, coronary heart disease and transplant rejection.

In the remainder of this session we will be looking in more detail at cell communication using chemical messengers. This is because intervening in the activity of chemical messengers, either by enhancing it, or more usually by blocking it, is a very fruitful way of developing new drugs.

2: Chemical messengers as a method of cell communication

Chemical signalling is a convenient way for cells to communicate. When a suitable cell is stimulated, it responds by releasing a chemical which diffuses through the tissue fluid. In order to detect and recognise these different chemical messengers, cells have evolved specialised protein molecules called receptors in their cell membranes. They usually respond by altering their shape when the messenger binds to active sites on the molecule.

The body uses chemical signalling in three ways:

- synaptic signalling
- endocrine signalling
- paracrine signalling.

Synaptic chemical signalling: chemical transmission between the cells in the nervous system and between nerve cells and other cells such as muscle cells.

Synaptic chemical signalling is the name given to chemical transmission between the cells in the nervous system and between nerve cells and other cells such as muscle cells. About twenty different chemicals are used as chemical messengers by different nerves, although the process is identical in all nerves.

Receptor: a specialised receiving agent located on the cell surface.

Synapse: a specialised gap or junction at nerve endings across which chemical transmission takes.

Neurotransmitter: a chemical messenger within the autonomic nervous system.

Endocrine chemical signalling: hormone secreting cells secrete their chemical messengers directly into the bloodstream.

Paracrine chemical signalling: chemical transmission between paracrine cells which release a local hormone and tissue cells close to the paracrine cell.

Stimulation of a nerve releases a chemical from the nerve ending which acts as a chemical messenger. The chemical transmitter diffuses across the small gap between the nerve ending and the next cell to act on specialised **receptors** on the cell surface. When the chemical messenger combines with its receptor it starts a series of events that leads to the cell responding in an appropriate way. The specialised gaps or junctions across which this type of chemical transmission takes place are called **synapses** and the chemical messengers are termed **neurotransmitters**.

In **endocrine chemical signalling**, hormone-secreting cells release their chemical messengers (hormones) directly into the bloodstream. The hormones travel in the blood to act on target cells that may be widely distributed throughout the body.

Paracrine chemical signalling also involves a hormone. In this case, specialised cells called paracrine cells release a 'local' hormone, but this only diffuses a short distance in the tissue to influence tissue cells close to the paracrine cell. These local hormones are not normally found in blood.

3: Revision of chemical transmission in the autonomic nervous system

There now follows a brief revision section on the autonomic nervous system. It is important to understand the basic concepts of chemical transmission between nerves and their effector organs because drugs that alter the normal process of synaptic transmission are those chosen for the treatment of most diseases.

The major physiological functions of the sympathetic and parasympathetic nervous system are given in Table 3. This is provided as a convenient summary that you can refer to, if necessary, as you work through the remainder of the course.

Organ	Sympathetic nervous system	Parasympathetic nervous system
heart	increased rate and force of contraction	decreased rate and force of contraction
smooth muscle of bronchioles	relaxation	contraction
smooth muscle of the pupil	dilation (mydriasis)	contraction (meiosis)

Organ	Sympathetic nervous system	Parasympathetic nervous system
gastro-intestinal tract	decreased peristalsis	increased peristalsis
smooth muscle of the bladder	relaxes; prevents urination	contracts; assists urination
bladder sphincters	contracts; prevents urination	relaxes; permits urination
metabolism	increases levels of glucose	none
blood vessel to the skin and viscera	constrict	none
blood vessels to muscle	dilates	none
adrenal gland	releases the hormone adrenaline	none
sweat glands	thick secretion	watery secretion
salivary glands	thick secretion	watery secretion
hair muscles	contraction	none

Table 3: *Functions of the autonomic nervous system*

The parasympathetic nervous system

The chemical transmitter in all sections of the parasympathetic nervous system is acetylcholine. Acetylcholine is located at the synapses in the parasympathetic ganglia and at the synapse at the end of the post-ganglionic parasympathetic nerve fibre. Acetylcholine acts on different types of receptors at these two sites.

In the ganglia, acetylcholine acts on a post-synaptic receptor called the nicotine receptor. It is called the nicotine receptor because the stimulant effects of acetylcholine on the post-ganglionic nerve are mimicked by nicotine. These receptors are blocked by ganglionic blocking drugs.

When we smoke we absorb nicotine that stimulates the autonomic ganglia. Nicotine stimulates the nicotinic receptors for acetylcholine and nerve impulses pass down the post-ganglionic nerve fibre to stimulate the end organs. Stimulation of the sympathetic ganglia raises blood pressure. One effect of stimulating parasympathetic ganglia is to increase the flow of saliva. Both of these effects are seen in smokers.

In the synapse at the post-ganglionic nerve ending, acetylcholine stimulates the contraction of smooth muscle or the secretion of glands by acting upon the muscarinic receptors. At this receptor site the actions of acetylcholine are mimicked by the drug muscarine, but not by nicotine. These receptors are blocked by atropine and similar drugs.

The sympathetic nervous system

The chemical transmitter at the post-ganglionic sympathetic nerve ending is noradrenaline. Stimulation of the sympathetic nervous system not only results in the release of noradrenaline from the post-ganglionic sympathetic nerve endings but also adrenaline from the medulla of the adrenal gland. When the hormone adrenaline is released into the bloodstream it has widespread effects throughout the body. These reinforce the effects of sympathetic nerve stimulation.

Activation of the sympathetic nervous system, and the release of adrenaline, are the major chemical messengers responsible for the increases in heart rate, sweating and the other physiological response that we associate with the stress response.

Different physiological responses to the same chemical transmitter and hormone are mediated by different receptors.

Contraction of smooth muscle (i.e. blood vessels, pupil of the eye). These effects are the result of stimulating alpha (a)-receptors located on the smooth muscle cells. The a-receptors are stimulated by the neurotransmitter noradrenaline, and less effectively by the hormone adrenaline.

Stimulation of both the force of contraction and heart rate. This effect is the result of stimulating a beta (ß)-receptor located on the heart muscle cells. This receptor is stimulated by adrenaline and is termed the ß1-receptor.

Relaxation of smooth muscle (i.e. blood vessels and bronchioles). This effect is the result of stimulating another type beta (ß)-receptor located on the smooth muscle cells. This receptor is stimulated by adrenaline and is termed the ß2- receptor.

Stimulation of the metabolism of stored fat to fatty acids. This effect is the result of stimulating a third type of ß-receptor located on fat cells. This receptor is also stimulated by adrenaline and is termed the ß3-receptor.

4: Classifying receptors

Receptors are classified according to the actions of the chemical messenger that stimulates them. One of the major research areas in pharmacology is the classification of the different types of receptors found in the body. The reason for this is that by understanding the response produced by stimulating the different types of receptors we can develop new drugs that are more selective in treating disease and that have fewer side-effects.

The precise classification of receptors is important for, as we have seen with acetylcholine and noradrenaline, there is often more than one type of receptor for each chemical messenger.

Sub-types of receptors

The major types of receptors can be divided into sub-types each of which responds differently to the same chemical messenger.

The classification of these different sub-types of receptors is not just a pharmacological curiosity; it has important implications for drug development. As each receptor sub-type is a different protein, encoded by a different gene, it should be possible to develop drugs that are selective for only one receptor sub-type. For example, adrenaline can act on all three receptor sub-types. It stimulates:

- the ß2 receptor, to relax smooth muscle. Drugs that stimulate this receptor are used to dilate the bronchiole smooth muscle during an asthmatic attack

- the ß1 receptor, which in turn stimulates the heart. Drugs that block this receptor are used in the treatment of angina

- the ß3 receptor, to increase fat metabolism. There are currently no drugs available that selectively stimulate this receptor. However, they are being developed as potential slimming agents.

The symptoms of many diseases result from a wrong or inappropriate response to a chemical messenger acting at one of its receptor sites. An understanding of how these different receptors produce different types of cellular response may enable us to design drugs that interact selectively with these receptors to reverse disease or reduce symptoms.

This approach to the development of new drugs has been successful over the last twenty years. Examples include:

- the development of the histamine H2 blocking drugs in the treatment of gastric and duodenal ulcers

- the ß1 blocking drugs for hypertension and heart disease

- ß2 stimulating drugs in the treatment of asthma

- the development of a new drug, sumatriptan, used in the treatment of migraine.