Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 16

Doctor Name: Dr. Yacoub

Written By: Mohammad abo Alia

SHEET ■

SLIDES □

DONE BY: ISSA KHASHAN

Autonomic Receptors

Types, Regulation and Action

The Autonomic Receptors

As we can find three types of neurons within the autonomic nervous system: cholinergic, adrenergic and dopaminergic, there are three corresponding types of receptors: cholinergic, adrenergic and dopaminergic. A substance is a neurotransmitter only if it has such receptors.

And as there are isoenzymes, there are subtypes of these receptors. For example, cholinergic receptors have two subtypes, and each one also has sub-subtypes. The other two types of receptors also have subtypes.

Cholinergic receptors can be stimulated in addition to acetylcholine (ACh) by two alkaloids, an alkaloid is a chemical name for a natural product (drug) that is *basic* in nature and of a natural origin – plants or animals. These two alkaloids are nicotine (found in tobacco) and muscarine (found in some kinds of poisonous mushrooms and other plants). Some subtypes of cholinergic receptors are stimulated by muscarine but not nicotine and are called muscarinic, while others are stimulated by nicotine and not muscarine and are called nicotinic.

This selectivity of receptors, muscarinic receptors for muscarine for instance, is not absolute, rather, it is relative. Muscarine *can* at high concentrations stimulate nicotinic receptors a little, and so does nicotine for muscarinic receptors. An application on this concept is that there are drugs that are "selective" for β1 receptors for example – Hold it! You will know what a β receptor is soon- and they reflect adverse effects similar to those of β2 receptors due to using a large dose. We lose the receptors' selectivity by changing to high concentrations.

Adrenergic receptors are stimulated by norepinephrine (NE) and other catecholamines. And the **dopaminergic** receptors are stimulated by dopamine.

Written by Mohamed F. Abu Alia

A deeper look at the subtypes:

Cholinergic receptors have two subtypes: muscarinic (M) and nicotinic (N).

Muscarinic receptors have five sub-subtypes: (it is important to know the location and function of these subtypes)

All subtypes (sub-sub) of muscarinic receptors can be found in CNS neurons, though we are more interested in those of the PNS.

M1: Sympathetic postganglionic neurons, and some presynaptic sites. The presence of these receptors on the sympathetic postganglionic neurons as heteroreceptors (that is receptors to other substances –here ACh- that regulate the function of a neuron) allows ACh to regulate the function of these neurons, along with being autoreceptors of ACh on the presynaptic sites.

M2: Smooth muscles (mainly) and myocardium and some pre-synaptic sites

M3: Exocrine glands, and vessels (the smooth muscle and the endothelium). Note that blood vessels don't have parasympathetic innervation (only sympathetic) but they have muscarinic receptors, they receive circulating ACh or cholinomimetics.

M4: Vagal nerve endings *(possibly)* with an unknown function.

M5: Vascular endothelium (not smooth muscle), especially cerebral vessels.

***keep in mind that all sub-types of muscarinic receptors are found in the CNS neurons**

Nicotinic receptors are more significant in the motor nervous system. In the autonomic nervous system, they are mainly in the ganglia, and the drugs that target ACh receptors in the ganglia are now obsolete. There is a subtype for the skeletal muscle endplate (N_M) –not part of the autonomic NS- and for neurons of the autonomic nervous system, mainly ganglia (N_N).

Adrenergic receptors also have two subtypes: alpha receptors with the α1 and α2 sub-subtypes, and beta receptors with the β1, β2 and β3 sub-subtypes.

α1: Postsynaptic effector cells especially smooth muscles (blood vessels, bronchi, GIT, urinary system, etc.)

α2: Mainly presynaptic autoreceptors mediating *negative* feedback (inhibition) of the release of NE. While presynaptic beta receptors (mainly β1) mediate *positive* feedback (stimulation) of NE release.

β1: Mainly the heart and the juxtaglomerular apparatus of renal tubules and ciliary body epithelium.

β2: Smooth muscles. (With some presynaptic receptors)

β3: Fat cells.

Dopaminergic receptors are mostly in the CNS. The autonomic dopamine receptors of the renal vascular bed (blood vessels) muscles are of the subtypes D1 and D5.

Regulation

Presynaptic Regulation:

Presynaptic autoreceptors (auto means self) that for cholinergic receptors mediate negative feedback and for adrenergic receptors mediate both negative feedback (α2) and positive feedback (beta). An autoreceptor for NE means that NE stimulates it, decreasing the release of NE (negative feedback) or increasing it (positive).

Heteroreceptors (hetero means different), a heteroreceptor for NE means that a substance other than NE stimulates the receptor affecting NE release.

Examples on heteroreceptors:

Some vagal fibers in the myocardium synapse on sympathetic noradrenergic nerve terminals and inhibit NE release. The sympathetic nerve fiber exiting the CNS (preganglionic) synapses with another nerve in a sympathetic ganglion and this second nerve (postganglionic) synapses with the effector organ. Another neuron (here, the vagal, a parasympathetic nerve) synapses on the presynaptic adrenergic terminal, a neurotransmitter is released from the vagus nerve (ACh) to the presynaptic terminal inhibiting the release of NE from this sympathetic nerve.

If only the cholinergic heteroreceptors of NE were found, and there is no nerves synapsing with the presynaptic terminal to provide ACh for regulation, circulating cholinomimetic substances (mimics the action of ACh) will bind these receptors and inhibit NE release.

Serotonin (5-hydroxytryptamine) a CNS neurotransmitter and also a hormone in the GIT. It can inhibit ACh release by the serotonin heteroreceptors of ACh on the

parasympathetic postganglionic nerve terminals. (The slides also mention that serotonin inhibits the release of ACh at preganglionic sites).

Adenosine and ATP (ATP is released along with other neurotransmitters) have receptors called purine receptors (P1 and P2, respectively). They *inhibit* adrenergic function (release of NE), meaning that their receptors are heteroreceptors for sympathetic postganglionic nerves.

Angiotensin II is the most potent vasoconstrictor in the body (meaning that a small amount can produce significant function). It *stimulates* adrenergic transmission.

Postsynaptic Regulation:

Up-regulation: is to *increase* the number of receptors in the cell, cause by *blocked* stimulation or lack of it, as in the exposure to an *antagonist*.

Down-regulation: is to *decrease* the number of receptors in the cell, caused by *over* stimulation, such as the exposure of an *agonist*.

So they both are mechanisms of cellular adaptation to stimulation or the lack of stimulation.

They both have a timeframe varying from seconds to days. What determines the time frame is the mechanism by which the regulation is made. In down-regulation that takes seconds, the cell *hides* the receptors to prevent agonist binding in a way similar to endocytosis (invagination of cell membrane). But in down-regulation that takes days, the cell inhibits protein synthesis inhibiting receptor synthesis, processing and insertion into the membrane of receptors, which takes days to produce effect. Or an enzyme comes and destroys the receptors in the case down-regulation, which takes minutes. In up-regulation, a receptor is already synthesized and not inserted in the membrane gets inserted, which takes minutes to hours.

The pharmaceutical importance of up and down regulation is that a blocker may be given to a patient causing up-regulation (having more receptors). Stopping the drug suddenly means that there is more receptors for the endogenous substances (the substances that the drug previously blocked their binding) and according to the law of mass action, there will be excessive binding creating more action, even if the amount of neurotransmitters is left unchanged. This will cause a condition called rebound, in which the abrupt withdrawal of taking the drug causes the condition, which the drug was preventing, to increase even further. For example, stopping an antihypertensive drug can make blood pressure even higher than before taking the drug. The solution here, is to draw these drugs gradually to reverse the up-

regulation. The drug is withdrawn in the same duration needed for up-regulation to happen .

Effects of Autonomic Nerve Activation

It is **extremely** important to memorize this whole table below

Direct effects of autonomic *nerve* activity on some organ systems. Autonomic *drug* effects are similar but not identical (see text).

	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
Organ	***Action*[1]**	***Receptor*[2]**	***Action***	***Receptor*[2]**
Eye				
Iris radial muscle	Contracts	α_1	…	…
Iris circular muscle	…	…	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	…	…
Contractility	Increases	β_1, β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	…	…
Skeletal muscle vessels	Relaxes	β_2	…	…
	[Contracts]	α	…	…
	Relaxes[3]	M_3	…	…
Endothelium of vessels in heart, brain, viscera	…	…	Synthesizes and releases EDRF[4]	M_3, M_5[5]
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	α_2, [6]β_2	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	…	…	Increases	M_3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant	Relaxes	β_2	…	…
	Contracts	α	Contracts	M_3
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscle	Contracts	α	…	…
Sweat glands			…	…
Eccrine	Increases	M	…	…
Apocrine (stress)	Increases	α	…	…
Metabolic functions				
Liver	Gluconeogenesis	β_2, α	…	…
Liver	Glycogenolysis	β_2, α	…	…
Fat cells	Lipolysis	β_3	…	…
Kidney	Renin release	β_1	…	…

[1]Less important actions are shown in brackets.

[2]Specific receptor type: α, alpha; β, beta; M, muscarinic.

[3]Vascular smooth muscle in skeletal muscle has sympathetic cholinergic dilator fibers.

[4]The endothelium of most blood vessels releases EDRF (endothelium-derived relaxing factor), which causes marked vasodilation, in response to muscarinic stimuli. Parasympathetic fibers innervate muscarinic receptors in vessels in the viscera and brain, and sympathetic cholinergic fibers innervate skeletal muscle blood vessels. The muscarinic receptors in the other vessels of the peripheral circulation are not innervated and respond only to circulating muscarinic agonists.

[5]Cerebral blood vessels dilate in response to M_5 receptor activation.

[6]Probably through presynaptic inhibition of parasympathetic activity.

Generally, these actions can be acquired be giving an agonist, reversed with antagonists, adverse effects are produced exaggeration of these actions.

A deeper look at this table:

The eye: it is affected by both the parasympathetic and the sympathetic NS. It has two main muscles:

The first is the iris that controls the size of the pupil, it is a muscular tissue with two muscles:

The iris circular muscle, it narrows the pupil when contracted and has parasympathetic innervation (M3).

The radial, it is attached to the outer border of the iris and it widens the pupil when contracted, it has sympathetic innervation (α1).

The second is the ciliary muscle that controls accommodation for vision, it is relaxed for far vision and is constricted for near vision. It has both, sympathetic (β) and parasympathetic (M3) innervation.

The heart: the sympathetic stimulation increases the strength and rate of heart contraction for fighting or flight. It mainly has (β1) receptors. The parasympathetic stimulation decelerates and reduces atrial contractility since it only innervates the atria and the SA node (through which the rate is reduced) and doesn't reach the ventricles, but affects them indirectly by affecting SA node firing (M2).

The blood vessels: Only have sympathetic innervation: (α) cause contraction in the smooth muscles and (β2) cause relaxation (vasodilation) which are predominant in the smooth muscles of the vascular bed of the skeletal muscles (and are abundant in the bronchial tree smooth muscles, which causes relaxation there, and thus, β2 stimulants are used for treating asthma). So with sympathetic stimulation where the heart rate and contractility is increased, more blood should flow to the skeletal muscles by vasodilation there.

Blood vessel endothelium has parasympathetic receptors (M3, M5) that once they get stimulated by ACh or cholinomimetics they release a substance called endothelium dependent/derived relaxing factor (EDRF) that relaxes blood vessels smooth muscles. EDRF is actually **nitric oxide (NO),** a lipid soluble gas that can diffuse through the endothelium to the smooth muscle and relax it.

GIT and GU smooth muscles: the important part here is the parasympathetic innervation , which is called here the secretomotor system. It stimulates increase in the *secretions* of the GIT and UT (urine), and it also stimulates the *contraction* in the wall causing urination and peristalsis in the GIT. In contrast, it stimulates sphincter muscle *relaxation.* All these effects together cause defecation in the GIT and urination in the UT.

In the uterus, the sympathetic stimulation is more important (β2, α), during pregnancy (α) and (M3) of the parasympathetic cause contraction in it. In certain cases, early contractions can occur before the fetus is in term, which threatens the pregnancy, in this case, we give β2 agonists that relax the uterus and prolong pregnancy.

In the sex organs, the parasympathetic (M) is responsible for erection and the sympathetic (α) is responsible for ejaculation.

Skin: sympathetic stimulation: sweat glands (M) in thermoregulatory sweating and (α) in the stress (apocrine). Piloerector smooth muscle (α) that contracts causing the hair of the skin to "erect"

Metabolism: the liver processes that produce glucose (gluconeogenesis and glycogenosis) mainly (β2), lipolysis (β3), renin release from the juxtaglomerular apparatus of the kidney (β1).

An extra note by the sheet writer for easier memorization:

Sympathetic: fight and flight: eyes for far vision β and wider pupil α1, faster and stronger heart β1 to run, vasodilation in muscles to move β2 and vasoconstriction in viscera α why would we need? relaxed bronchi β2 to breath, relaxed walls of GIT α2 and bladder β2 and contracted sphincters α1 we don't eat, hair standing and more sweating α we are scared, and more sugar please β2 and β3.

Parasympathetic: eat and rest: eyes for near vision and small pupil M3 why to see? Heart is slow and atria weak M2 to rest and sleep, NO here to relax your vessels M3, 5. Bronchi contracted M3 to breathe deep, walls contracted sphincters relaxed more secrete M3 just to eat! And keep the rest rest please :)

Good Luck

A WITTY QUOTE PROVES NOTHING

- VOLTAIRE