Autonomic Pharmacology:
Actions of parasympathetic system

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Last update: 23.01.2013

1

Cholinoceptors

- Cholinoceptors are members of either G protein–linked (muscarinic) or ion channel (nicotinic) families on the basis of their transmembrane signaling mechanisms.

2

Cholinoreceptors

Cholinoceptors		
Muscarinic M_1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP_3 and DAG, increased intracellular calcium
Muscarinic M_2	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M_3	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M_1 receptor-ligand binding
Muscarinic M_4	CNS neurons; possibly vagal nerve endings	Like M_2 receptor-ligand binding
Muscarinic M_5	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M_1 receptor-ligand binding
Nicotinic N_N	Postganglionic neurons, some presynaptic cholinergic terminals	Opening of Na^+, K^+ channels, depolarization
Nicotinic N_M	Skeletal muscle neuromuscular endplates	Opening of Na^+, K^+ channels, depolarization

3

Muscarinic receptors

- Muscarinic receptors contain seven transmembrane domains whose third cytoplasmic loop is coupled to G proteins that function as transducers.
- Muscarinic receptors are located on plasma membranes of cells in the central nervous system, in organs innervated by parasympathetic nerves as well as on some tissues that are not innervated by these nerves, eg, endothelial cells, and on those tissues innervated by postganglionic sympathetic cholinergic nerves.

4

Nicotinic receptors

- Nicotinic receptors are part of a transmembrane polypeptide whose subunits form cation-selective ion channels.
- These receptors are located on plasma membranes of postganglionic cells in all autonomic ganglia, of muscles innervated by somatic motor fibers, and of some central nervous system neurons.

5

Effects of Direct-Acting Cholinoceptor Stimulants (1/2)

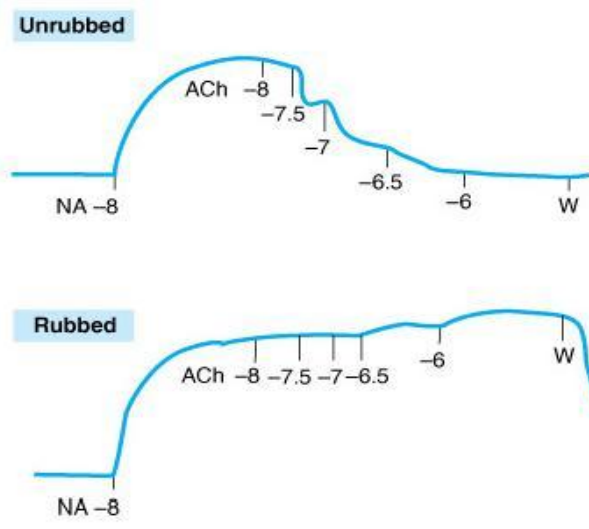
Organ	**Response**
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries	Dilation (via EDRF). Constriction (high-dose direct effect)
Veins	Dilation (via EDRF). Constriction (high-dose direct effect)

6

Effects of Direct-Acting Cholinoceptor Stimulants (2/2)

Organ	Response
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

7



Source: Katzung BG: *Basic & Clinical Pharmacology*, 10th Edition: http://www.accessmedicine.com

8

Autonomic Ganglia

- The primary pathway of cholinergic transmission in autonomic ganglia is similar to that at the neuromuscular junction of skeletal muscle.
- Ganglion cells can be discharged by injecting very small amounts of ACh into the ganglion. The initial depolarization is the result of activation of nicotinic ACh receptors, which are ligand-gated cation channels with properties similar to those found at the neuromuscular junction.
- Several secondary transmitters or modulators either enhance or diminish the sensitivity of the postganglionic cell to ACh.

9

Actions of Acetylcholine at Prejunctional Sites (1/2)

- Both cholinergic and adrenergic nerve terminal varicosities contain autoreceptors and heteroreceptors.
- ACh release therefore is subject to complex regulation by mediators, including ACh itself acting on M_2 and M_4 autoreceptors, and other transmitters (*e.g.*, norepinephrine acting on α_{2A}- and α_{2C} adrenergic receptors) or substances produced locally in tissues (*e.g.*, NO).

10

Actions of Acetylcholine at Prejunctional Sites (2/2)

- At some neuroeffector junctions such as the myenteric plexus in the GI tract or the SA node in the heart, sympathetic and parasympathetic nerve terminals often lie juxtaposed to each other.
- The opposing effects of norepinephrine and ACh, therefore, result not only from the opposite effects of the two transmitters on the smooth muscle or cardiac cells but also from the inhibition of ACh release by norepinephrine or inhibition of norepinephrine release by ACh acting on heteroreceptors on parasympathetic or sympathetic terminals.

11

Cardiovascular System

- ACh has four primary effects on the cardiovascular system: vasodilation, a decrease in cardiac rate (the negative chronotropic effect), a decrease in the rate of conduction in the specialized tissues of the sinoatrial (SA) and atrioventricular (AV) nodes (the negative dromotropic effect), and a decrease in the force of cardiac contraction (the negative inotropic effect).
- The last effect is of lesser significance in ventricular than in atrial muscle. Certain of the above responses can be obscured by baroreceptor and other reflexes that dampen the direct responses to ACh.

12

Gastrointestinal and Urinary Tracts

- Although stimulation of vagal input to the gastrointestinal tract increases tone, amplitude of contraction, and secretory activity of the stomach and intestine, such responses are inconsistently seen with administered ACh.
- Poor perfusion of visceral organs and rapid hydrolysis by plasma butyrylcholinesterase limit access of systemically administered ACh to visceral muscarinic receptors.
- Parasympathetic sacral innervation causes detrusor muscle contraction, increased voiding pressure, and ureter peristalsis, but for similar reasons these responses are not evident with administered ACh.

13

Extraneuronal Cholinergic Systems

- ACh is present in the vast majority of human cells and organs, including epithelial cells (airways, alimentary tract, epidermis, glandular tissue), mesothelial and endothelial cells, circulating cells (platelets), and immune cells (mononuclear cells, macrophages).
- Although the exact function of non-neuronal ACh is not known precisely, proposed roles include the regulation of elementary cell functions such as mitosis, locomotion, automaticity, ciliary activity, cell-cell contact, barrier function, respiration and secretion, and regulation of lymphocyte function.

14

Tablo 4.1 Otonom sinir sisteminin önemli etkileri (akt., aktivite).

Organ	Sempatik akt.	Reseptör	Parasempatik akt.	Reseptör
Kalp				
Sinoatrial nod	Hız ↑	β_1, β_2	Hız ↓	M_2
Atrium kası	Güç ↑	β_1, β_2	Güç ↓	M_2
AV nod	Otomatisite ↑	β_1, β_2	İleti hızı ↓, AV blok	M_2
Ventrikül kası	Otomatisite, güç ↑	β_1, β_2	Etki yok	
Kan damarları				
Arterioller				
Koroner damarlar	Dilatasyon	β_2	Etki yok	
İskelet kası	Kontraksiyon	α		
	Dilatasyon	β_2, M	Etki yok	
Organlar, deri, beyin	Kontraksiyon	α	Etki yok	
Erektil doku	Kontraksiyon	α	Dilatasyon	M_3
Salgı bezi	Kontraksiyon	α	Dilatasyon	M_3
Venler	Kontraksiyon	α	Etki yok	
	Dilatasyon	β		
Damar endoteli			NO salıverdirir	M_3
Bronşlar				
Düz kas	Dilatasyon	β_2	Kontraksiyon	M_3
Salgı bezleri	Etki yok		Sekresyon	M_3
GİS				
Duvar düz kası	Relaksasyon	α_2, β_2	Motilite ↑	M_3
Sfinkter düz kası	Kontraksiyon	α_1, β_2	Dilatasyon	M_3
Salgı bezleri	Etki yok		Dilatasyon	M_3
			Sekresyon	M_3
			Asit salgısı	M_1
Miyenterik pleksus	İnhibe eder	α	Aktive eder	M_1
Uterus				
Hamile	Kontraksiyon	α	Değişken	M_3
Hamile olmayan	Relaksasyon	β_2		
Penis	Ejekülasyon	α	Ereksiyon	M_3
Göz				
İris radyal kası	Kontraksiyon	α_1		
İris sirküler kası			Kontraksiyon	M_3
Silier kas	Relaksasyon	β	Kontraksiyon	M_3
Deri				
Ter bezleri				
Termoregülatuar	Sekresyon	M	Etki yok	
Apokrin	Sekresyon	α	Etki yok	
Pilomotor	Piloereksiyon	α	Etki yok	
Salgı bezleri	Sekresyon	α, β	Sekresyon	M_3
Gözyaşı bezleri	Etki yok		Sekresyon	M_3
Böbrek	Renin sekresyonu	β_1	Etki yok	
Karaciğer	Glikojenoliz, glikoneogenez	β_2, α	Etki yok	
Pankreas	İnsülin salınması	$\alpha_2 \downarrow$, $\beta_2 \uparrow$		
Yağ hücreleri	Lipoliz	β_3		
Otonom sinir uçları				
Sempatik	Noradrenalin salınmasının azaltılması	α_2	Noradrenalin salınmasının azaltılması	M_1, M_2
Parasempatik	Asetilkolin salınmasının azaltılması	α	Asetilkolin salınmasının azaltılması	M_2

15

Thank you...

16