**Autonomic Drugs -Summaries**

**Cholinomimetic Agents**  Cholinomimetics can mimic some or all of the effects of endogenous acetylcholine (ACh).  ACh acts on all of the cholinergic receptor subtypes. **Names of agents in bold type may be used on exams.**  
**Major effects** associated with stimulation of cholinergic receptors are underlined; **major implications for dentistry in italics**

Muscarinic agonists: Act directly on effector tissues on postjunctional receptors (available agents are non-selective for the various subtypes of muscarinic receptors). These agents exert the same effects that are caused by acetylcholine on tissues innervated by parasympathetic nerves; and, in addition, they cause vasodilatation indirectly via release of nitric oxide from vascular endothelial cells. In other words, muscarinic agonists are parasympathomimetics, and will cause all of the peripheral effects coded by the mnemonic, DUMBBELSS except for excitation of skeletal muscle. When administered systemically, they cause many effects other than the desired effect because of the wide distribution of muscarinic receptors. Pilocarpine and cevimeline can be used to stimulate salivary flow in patients with xerostomia. Xerostomia can be caused by irradiation of the neck and face and by Sjögren’s syndrome.

For a summary of the effects of the parasympathetic and sympathetic nervous systems on the various autonomically-innervated tissues/cells, see p. 73 of Yagiela et al. , 4th Ed. ; p. 87 in 5th Ed.

Drugs to know: **bethanechol, pilocarpine, cevimeline**

Indirectly acting cholinomimetics: Inhibitors of acetylcholinesterase will cause buildup of ACh concentrations at all sites where ACh is released from cholinergic nerves.  Thus, these agents can stimulate skeletal muscle, stimulate ganglionic transmission (i.e. depolarize postganglionic nerves of both the PNS and SNS; therefore, causing effects associated with both of these systems), cause adrenal release of epinephrine, and also accentuate muscarinic effects due to buildup of ACh at the effector cells (provided that nerve traffic in the postganglionic parasympathetic nerve is not blocked in some manner; ACh levels cannot build up in synapses if it is not released). Central effects of cholinergic nerve stimulation can be caused if the ACh esterase inhibitor is able to get into the brain. **A patient being treated for Alzheimer's disease may be taking an ACh esterase inhibitor, donepezil** (which can be distributed to the CNS). If skeletal neuromuscular junction blockers (considered in a future lecture) are used along with a general anesthetic during oral surgery, an ACh esterase inhibitor might be used to reverse the effect of the NMJ blocker (if the NMJ blocker is of the competitive-type; see future lecture). **Physostigmine** has a tertiary nitrogen in its structure and is uncharged at physiological pH (thus it can get into the CNS), unlike **neostigmine**, which is a quaternary N-containing compound. Physostigmine can be used to treat poisoning by muscarinic antagonists like atropine that are distributed to the CNS. Since atropine acts as a competitive pharmacological antagonist, its effect can be antagonized by ACh, which competes with it for muscarinic receptors. Physostigmine causes a buildup of endogenous ACh levels wherever it is released.

Drugs to know: **neostigmine, physostigmine, donepezil**

Cholinergic blocking agents:
**Muscarinic antagonists:** Block ACh action on muscarinic receptors at tissues receiving postganglionic parasympathetic nerves and postganglionic sympathetic nerves innervating sweat glands. Result: absence of effects normally associated with tonic (or increased) influence of ACh on these tissues.

Drugs to know: atropine, scopolamine, benztropine or trihexyphenydil (used for CNS effect in Tx of Parkinson's disease), ipratropium or tiotropium (used chronically by some patients with chronic obstructive pulmonary disease; i.e. COPD), glycopyrrolate (useful during surgery to decrease secretions), tolterodine (used chronically by some patients with incontinence due to “overactive bladder”), diphenhydramine (used in OTC sleep-aid preparations, as antihistamine, to Tx motion sickness, and as an anti-emetic – used to help treat cancer chemotherapy-induced vomiting).

You might use scopolamine and/or glycopyrrolate acutely in surgery to supplement anesthesia (scopolamine) and to reduce flow of saliva. You might see patients who present with systemic blockade of muscarinic receptors because they are receiving scopolamine for motion sickness, benztropine or trihexyphenydil for Parkinson's disease or tolterodine for Tx of urinary incontinence. Although diphenhydramine is categorized as an antihistamine, it is a potent muscarinic antagonist also. Muscarinic antagonists cause xerostomia, which may account for poor dental health. These patients can be photophobic. Reflex bradycardia (which normally accompanies the effects of injected sympathomimetics that exert pressor effects, i.e. increased arterial pressure) will be blocked (because increased ACh release accounts for reflex bradycardia [ACh acts to cause reflex bradycardia by binding to cardiac M_2 receptors]; therefore, inadvertent injection of sympathomimetic agents is more likely to cause cardiac stimulation (provided that the sympathomimetic binds to beta receptors, e.g. epinephrine, norepinephrine) and exaggerated pressor effects.

**NMJ blocking agents:** Blockade of ACh effect on skeletal muscle (to be covered in future lecture).

**Ganglionic Agents:**

Drugs to know: nicotine, varenicline, mecamylamine

You might see patients taking mecamylamine (which blocks ganglionic transmission) as part of smoking cessation programs. These patients might exhibit photophobia, orthostatic hypotension and xerostomia. Baroreceptor-mediated changes in heart rate will be blocked. (see above: as with muscarinic blockers, because the efferent limb of the reflex arc involves ganglionic transmission). The ganglion-blocked patient will still respond to injected sympathomimetics. In fact, the effect of sympathomimetics will be accentuated in a patient who is taking a ganglionic blocking agent (because baroreceptor reflexes are blocked).

You might see patients who are taking varenicline chronically for smoking cessation. Remember that this agent is a partial nicotine receptor agonist (remember from principles that a partial agonist can act as an antagonist). About the only troublesome peripheral effects of varenicline reported to date are nausea and constipation.

**Sympathomimetic Agents:**
Prototype examples of sympathomimetic amines are:
epinephrine - agonist at alpha sub 1 , alpha sub 2 , beta sub 1 and beta sub 2 receptors
norepinephrine - agonist at alpha sub 1 , alpha sub 2 , and beta sub 1 receptors
isoproterenol - agonist at beta sub 1 and beta sub 2 receptors
dopamine - agonist at dopamine receptors (DA sub 1 and DA sub 2 ), beta sub 1 and alpha sub 1 receptors (higher doses)

Listed below are prototype sympathomimetics (agonists) with the following information in order: adrenergic receptor subtype activated ; prototype agent ; major effects associated with their stimulation; major implications for dentistry

Agents that act primarily via direct-action on adrenergic receptors

alpha sub 1 : phenylephrine (Neosynephrine TM ), a selective agonist at alpha sub 1 receptors; vasoconstriction, dilation of pupil; employed as vasoconstrictor in local anesthetic solutions, safer for use in cardiac patients than agents with beta activity; powerful alpha agonists can be used for hemostasis, e.g. alpha activity of epinephrine. Is metabolized by MAO, not by COMT, therefore its use should be avoided in patients taking MAO inhibitors (because the vasoconstrictor effect could be potentiated). Patients may be using topical, over-the-counter preparations of this agent as a nasal decongestant.

alpha sub 2 ; clonidine and alphamethyl norepinephrine (levonordefrin); action on receptors in vasomotor center (central nervous system) decreases sympathetic outflow from the vasomotor center to heart and vessels -> hypotension; CNS effect also causes sedation; action on presynaptic membrane of autonomic nerves -> reduced transmitter release; direct action on peripheral blood vessels --> vasoconstriction ; (note: the vasoconstrictor effect is what is exploited in the use of levonordefrin in local anesthetic solutions); patients taking oral clonidine or alpha methylDOPA (precursor of the false transmitter alphamethyl norepinephrine) for high blood pressure may show a additive response to sedatives. Also, clonidine causes significant xerostomia.

beta sub 1 ; dobutamine (cardiovascular effects are primarily due to action on beta sub 1 receptors) stimulation of cardiac tissues, increasing heart rate, conduction velocity and contractility; when using agents with beta sub 1 agonist activity, use extreme caution in cardiac patients. While this agent is unlikely to be used in the outpatient dentistry arena, you should be aware that agents with beta sub 1 agonist activity foster cardiac arrhythmias, particularly in the presence of hyperthyroidism, in patients taking digitalis and in the presence of some general anesthetics.

beta sub 2 ; albuterol; relaxation of vascular, bronchiolar and uterine smooth muscle cells, breakdown of glycogen to glucose (if given systemically); For termination of acute attacks of asthma, beta sub 2 agonists afford the most rapid and efficacious treatment. An inhaler dosage form of this type of sympathomimetic should be available for such patients. Inhalation route of administration restricts the agent’s effects primarily to the lung.

salmeterol (beta sub 2 selective agonist): This slow-acting, long-acting compound is used for chronic treatment of asthma, not for termination of acute attacks. Side effects are minimal, may include tachycardia and tremor.
Multiple receptors, not a selective agonist; **dopamine**; vasodilation of kidney arterioles; dopamine can be used to **stimulate cardiac output** (via its beta 1 activity) to support the circulation during surgery (while preserving renal blood flow). It will also cause **vasoconstriction with higher doses**.

Use of vasoconstrictors with local anesthetics (LA):

- **rationale**- a) such use can reduce the total dose necessary for the LA to exert its desired effect; LA are potentially toxic; (vasoconstrictor delays systemic absorption of the LA from the site of injection, thus the local concentration of the LA is kept higher), b) prolongs duration of action of the LA

- epinephrine - is the most potent sympathomimetic vasoconstrictor, has substantial beta 1 agonist activity; dose should be reduced to 1/5 - 1/4 normal levels in patients with heart disease. Pressor effect is increased in the presence of non-selective beta receptor blockade (which prevents epi’s beta 2 agonist effect, which normally causes vasodilation of skeletal muscle vessels).

  Also, note that in patients who may be treated systemically with a muscarinic receptor antagonist (e.g. tolterodine, for incontinence), the reflex bradycardia associated with blood pressure elevation will be blocked, thus exaggerating the pressor sympathomimetics.

**Indirectly acting agents:** Act via release of NE from nerve ending stores; therefore their effects are those of norepinephrine; intact neuronal stores of NE are needed in order for these to act. Examples: **amphetamine** (note: can get into the CNS, unlike injected NE.); **tyramine**

**Sympatholytics:**

Agents acting as pharmacological antagonists: occupy postjunctional receptors, lack efficacy, compete with endogenous NE and EPI for adrenoceptors.

**Alpha adrenoceptor antagonists:** examples: **prazosin, tamsulosin**

  - block effects of endogenous NE and EPI that are exerted via alpha receptors: i.e. alpha blockers will decrease arteriolar and venous constriction, decrease load on the heart by decreasing vascular resistance, may cause reflex tachycardia, decrease resistance to urinary outflow.

  - will block the alpha 1-mediated vasoconstrictor effect of sympathomimetics included in local anesthetic solutions; can cause orthostatic hypotension. **Note that levonordefrin (alpha 2 agonist) will still be effective in patients treated with alpha 1 blockers.**

**Beta adrenoceptor antagonists:** examples: **propranolol** (non-selective block of beta receptors), **metoprolol** ("selective" beta 1 blockade), **carvedilol** (block of α 1 and β receptors)

  - block cardiac and metabolic effects of sympathomimetics with beta agonist activity, decrease blood pressure (after chronic use); decrease work load on the heart, non-selective beta blockers reduce beta 2-mediated relaxation of smooth muscle and thus can aggravate asthma (due to loss of the effect of circulating epinephrine on beta 2 receptors on bronchioles)
- blockade of beta₂ receptors will cause exaggeration of the pressor effect of epinephrine that reaches the bloodstream.

**Agents acting at the sympathetic nerve ending:** Note*: These agents can be either sympatholytics or sympathomimetics (e.g. cocaine and, in certain circumstances, MAO inhibitors).

  - **guanethidine** and **bretylium** - inhibit nerve action potential-induced release of NE → sympatholytic effect; **reserpine** - inhibits storage of NE in the vesicle → depletion of NE stores → sympatholytic effect

  General effects of these agents: global, peripheral decrease/loss of SNS function. **Caution:** receptor responsiveness to injected sympathomimetics remains and is often enhanced. Reserpine will also have CNS effects (depressant). In tissues with both PNS and SNS innervation, events associated with PNS stimulation will be dominant. Since the SNS support of vasoconstriction is lost (dilating veins as well as arterioles) these agents cause **orthostatic hypotension**. Use caution with movement of patient from supine to upright position.

  - **cocaine** - blocks Uptake I (re-uptake of NE into nerve ending) → sympathomimetic effect

  **MAO inhibitors** (don’t need to know individual drug names at this time) – can cause decreased NE biosynthesis and formation of a low-efficacy "false transmitter", resulting in decreased sympathetic function, i.e. sympatholytic. Chronic treatment can cause **Orthostatic hypotension**. However, ingestion of tyramine-containing foods or injection of an indirectly acting sympathomimetic (causing sudden release of remaining, stored NE) can cause a dangerous elevation in blood pressure, i.e. a sympathomimetic effect.

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**Use of knowledge practice:** Clinical correlation / “Case” / vignette

The patient is a 59 yr. old male. He is being treated chronically with **tamsulosin** for benign prostatic hyperplasia and also with **carvedilol** as part of the overall treatment of congestive heart failure (CHF), the latter being complicated by ischemic heart disease (manifest by occasional attacks of angina). The dentist scheduled to treat this patient is concerned that the local anesthetic (LA) to be employed, if absorbed from the injection site, might depress cardiac contractility and/or alter cardiac rhythm in this patient.

Pharmacologic implications / questions (assume that the doses of both tamsulosin and carvedilol are sufficient to provide effective plasma levels of these drugs at the time of the dental procedure):

1) **What is a pharmacological approach that can be used to reduce/prevent systemic toxicity of the LA?**

2) **What type of drug is tamsulosin? Carvedilol?** These agents bind to ________ receptors?
3) What side effect(s) might be caused by these agents? What caution(s) must be considered?

4) Would epinephrine be likely to cause cardiac tachyarrhythmias in this patient? Will epinephrine be likely to cause an exaggerated pressor effect in this patient?

5) Considering your answer to question #1, what drug might be used to afford the desired effect?

For discussion of the case, after you work on this, see separate file – “Clinical Case Ans”