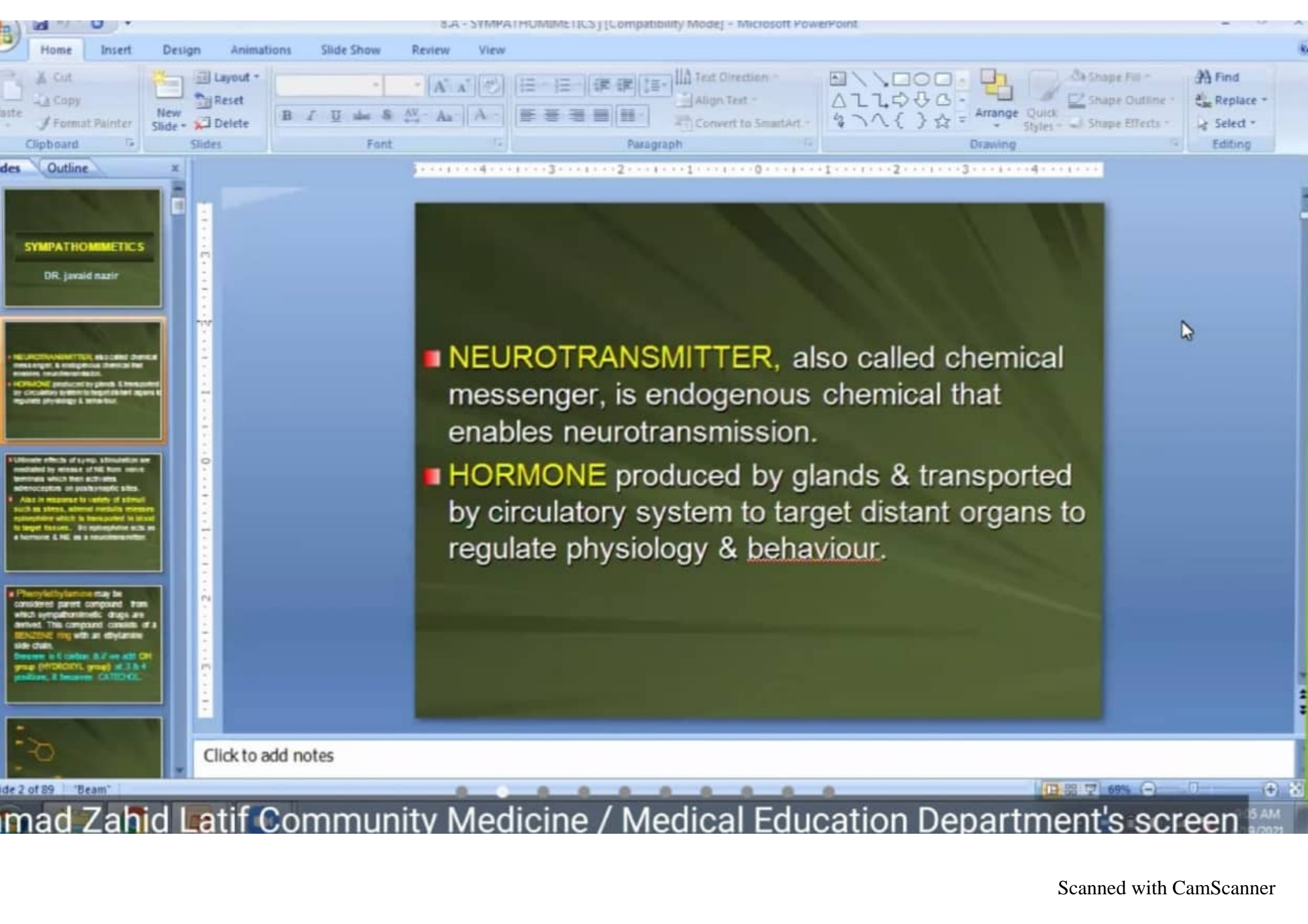


SYMPATHOMIMETICS

DR. iavaid nazir

IF From Ihtisham F18-052 to Everyone

F18-052



SYMPATHOMIMETICS

DR. javaid nazir

- **NEUROTRANSMITTER**, also called chemical messenger, is endogenous chemical that enables neurotransmission.
- **HORMONE** produced by glands & transported by circulatory system to target distant organs to regulate physiology & behaviour.

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Microsoft PowerPoint interface showing a slide titled "SYMPATHOMIMETICS" by DR. javaid nazir. The slide content is as follows:

- Ultimate effects of symp. stimulation are mediated by release of NE from nerve terminals which then activates adrenoceptors on postsynaptic sites.
- Also in response to variety of stimuli such as stress, adrenal medulla releases epinephrine which is transported in blood to target tissues. So epinephrine acts as a hormone & NE as a neurotransmitter.

Additional text visible in the slide's left sidebar:

- NEUROTRANSMITTER, also called chemical messenger, & endogenous chemical that enables neurotransmission.
- HORMONE produced by glands & transported by circulatory system to target distant organs to regulate physiology & behaviour.
- Ultimate effects of symp. stimulation are mediated by release of NE from nerve terminals which then activates adrenoceptors on postsynaptic sites.
- Also in response to variety of stimuli such as stress, adrenal medulla releases epinephrine which is transported in blood to target tissues. So epinephrine acts as a hormone & NE as a neurotransmitter.
- Phenylethylamine may be considered parent compound from which sympathomimetic drugs are derived. This compound consists of a BENZENE ring with an ethylamine side chain. Benzene is 6 carbon & if we add OH group (HYDROXYL group) at 3 & 4 positions, it becomes CATECHOL.

Slide 3 of 89 | "Beam" | 69%



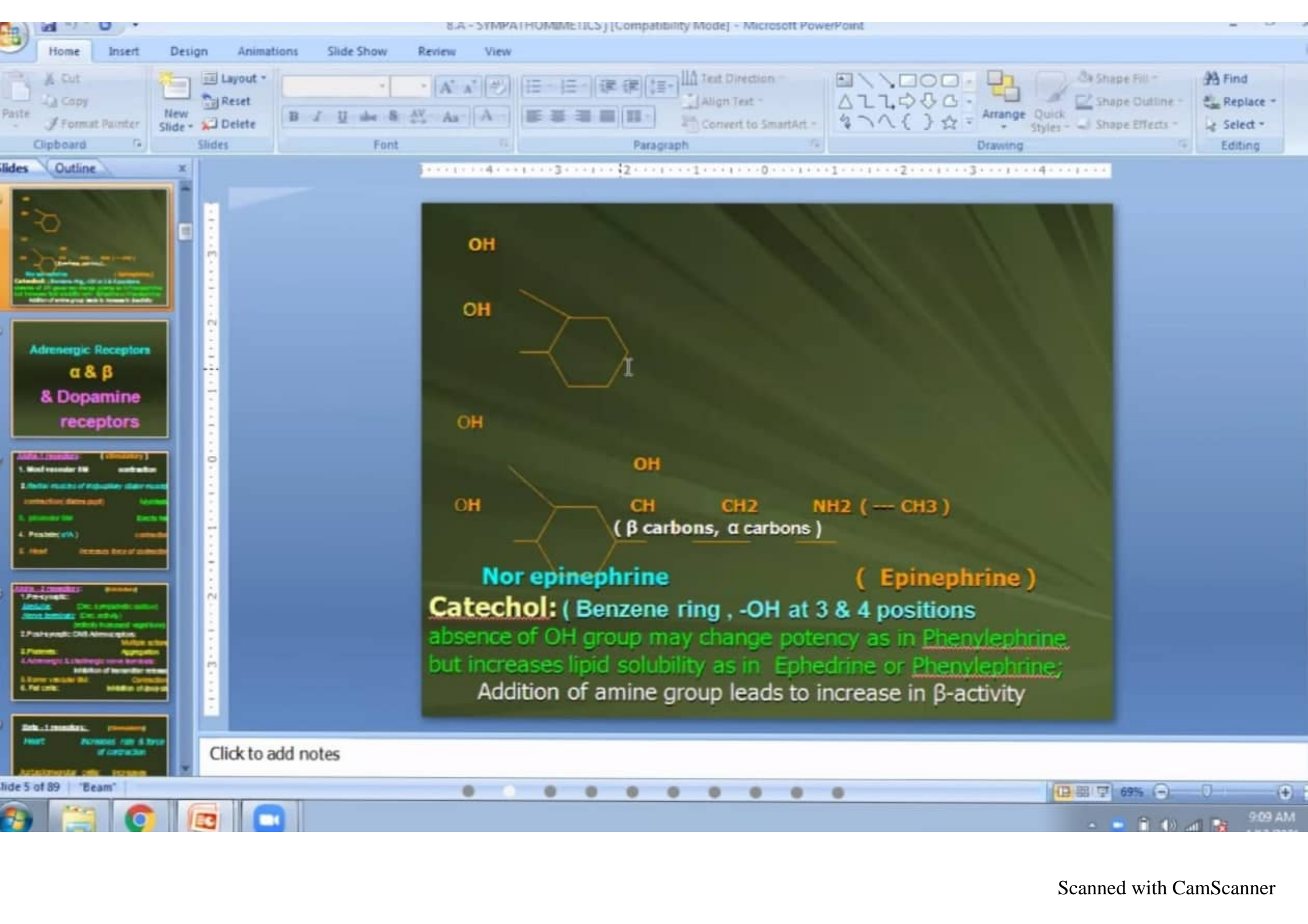
Slides Outline

- SYMPATHOMIMETICS
- DR. javaid nazir
- NEUROTRANSMITTER, associated chemical messengers, & endogenous chemical that enables neurotransmission.
- HORMONE produced by glands, & transported by circulatory system to target distant organs to regulate physiology & behaviour.
- Ultimate effects of a symp. stimulation are mediated by release of NE from nerve terminals which then activates adrenoceptors on postsynaptic sites.
- Also in response to variety of stimuli such as stress, adrenal medulla releases epinephrine which is transported in blood to target tissues. In epinephrine acts as a hormone & NE as a neurotransmitter.
- Phenylethylamine may be considered parent compound from which sympathomimetic drugs are derived. This compound consists of a BENZENE ring with an ethylamine side chain. Benzene is 6 carbon & if we add OH group (HYDROXYL group) at 3 & 4 positions, it becomes CATECHOL.

■ Phenylethylamine may be considered parent compound from which sympathomimetic drugs are derived. This compound consists of a **BENZENE ring** with an ethylamine side chain.

Benzene is 6 carbon & if we add OH group (HYDROXYL group) at 3 & 4 positions, it becomes CATECHOL.

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OH

OH

OH

OH

OH

CH (β carbons, α carbons)

CH₂

NH₂ (— CH₃)

Nor epinephrine

(Epinephrine)

Catechol: (Benzene ring , -OH at 3 & 4 positions

absence of OH group may change potency as in Phenylephrine
but increases lipid solubility as in Ephedrine or Phenylephrine;

Addition of amine group leads to increase in β-activity

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Alpha - 2 receptors: (Inhibitory)

1. Pre-synaptic:

Medulla: (Dec. sympathetic outflow)

Nerve terminals: (Dec. activity)

(reflexly increased vagal tone)

2. Post-synaptic CNS Adrenoreceptors:

Press ESC or double-click to exit full screen mode

Multiple actions

3. Platelets: Aggregation

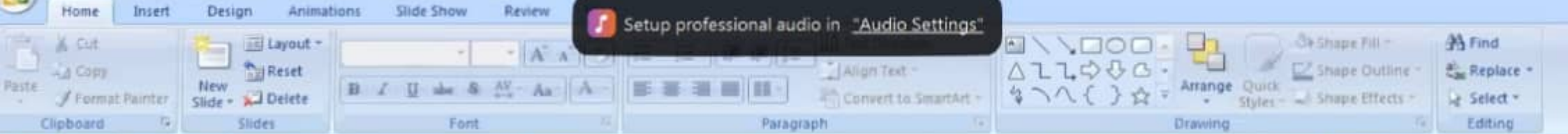
4. Adrenergic & cholinergic nerve terminals: Inhibition of transmitter release.

5. Some vascular SM: Contraction

6. Fat cells: inhibition of *lipolysis*

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Slides Outline

- Slide 1: Introduction
- Slide 2: Beta-1 receptors
- Slide 3: Beta-2 receptors
- Slide 4: Dopamine receptors

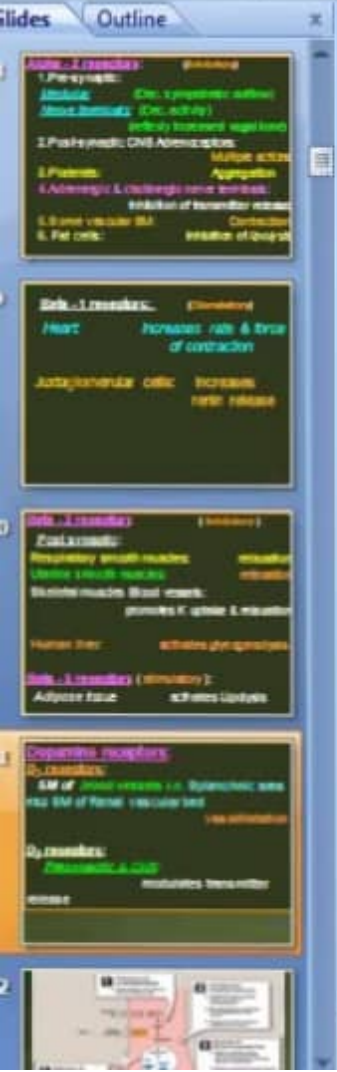
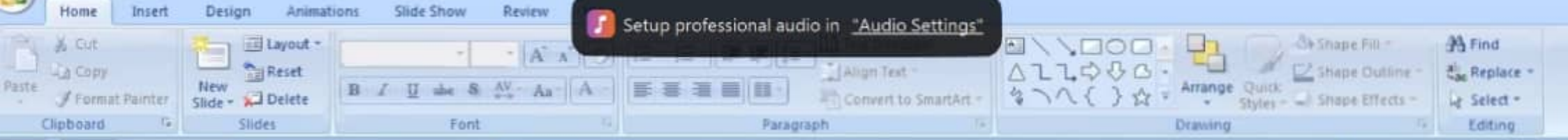
Beta - 1 receptors: **(Stimulatory)**

Heart: *Increases rate & force of contraction*

Juxtaglomerular cells: Increases renin release

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Dopamine receptors:

D₁ receptors:

SM of blood vessels i.e. Splanchnic area
esp SM of Renal vascular bed
vasodilatation

D₂ receptors:

Presynaptic & CNS:
modulates transmitter
release

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Slides Outline

CLASSIFICATION

1. According to chemical structure

CATECHOLAMINES

1) NATURAL

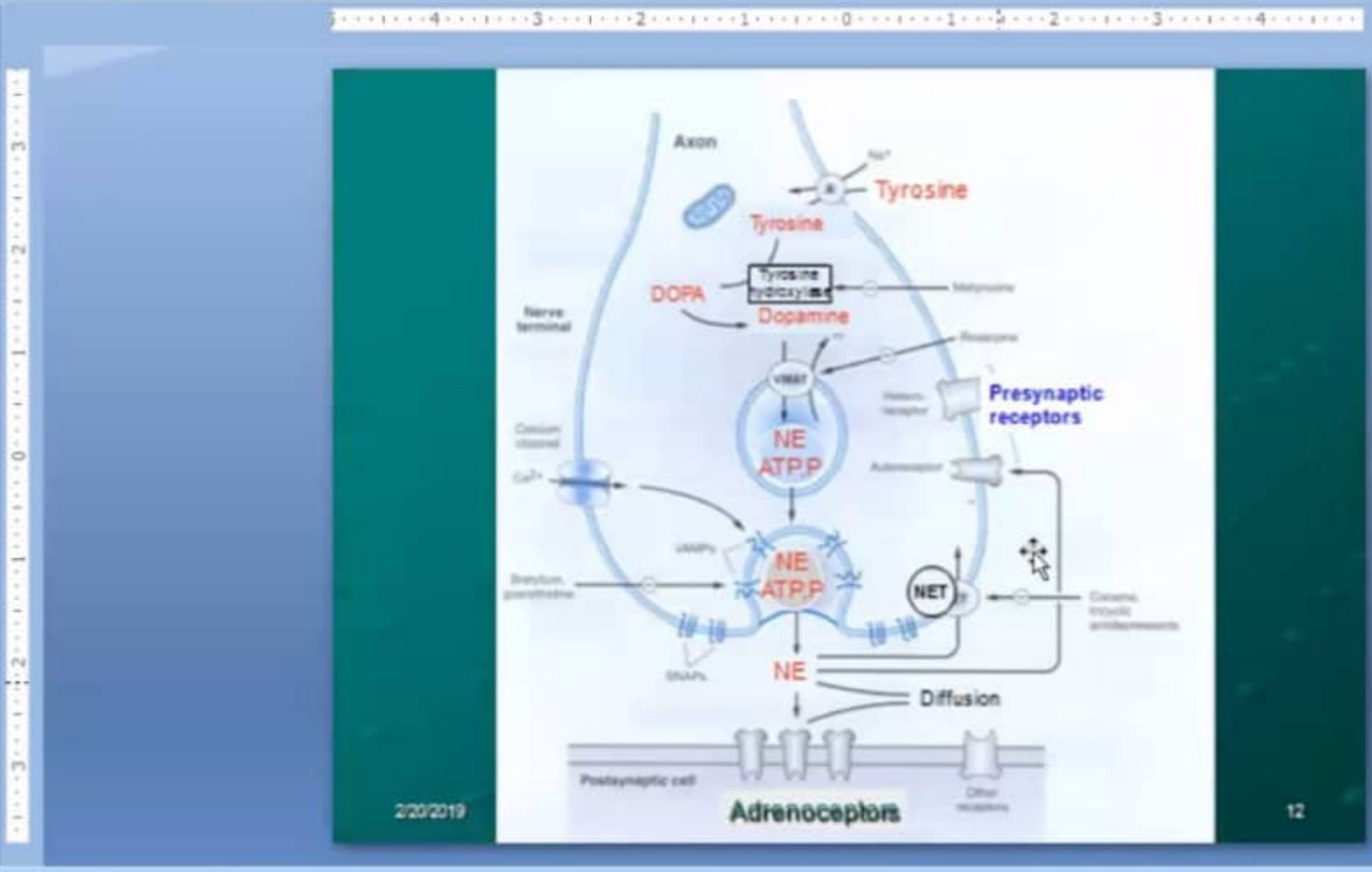
1. Epinephrine
2. Nor epinephrine
3. Dopamine

2) SYNTHETIC

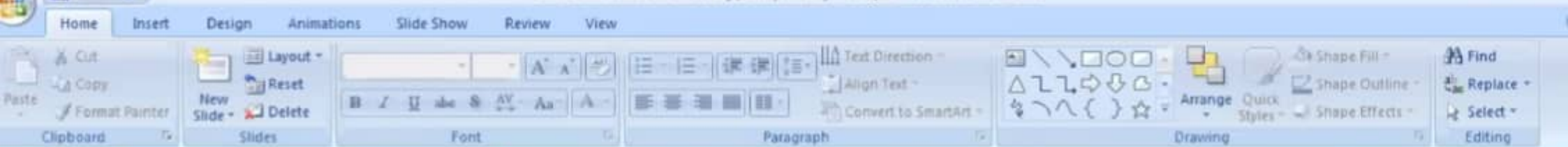
1. Dopamine
2. Isoproterenol

2. According to effect

1. Phenylephrine
2. Naphazoline
3. Ephedrine
4. Amphetamine
5. Desmethamphetamine
6. Methamphetamine



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Slides Outline

1. *Aspirin, a chemical structure*

CATECHOLAMINE

- 1) NATURAL
 - 1.2 Dopamine
 - 3. Nor epinephrine
 - 3. Dopamine
- 2) SYNTHETIC
 - 1. Dopamine
 - 2. Isoproterenol

4. NON-CATECHOLAMINE

- 1. Phenylephrine
- 2. Norepinephrine
- 3. Epinephrine
- 4. Isoproterenol
- 5. Dobutamine
- 6. Terbutaline

CLASSIFICATION

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I. According to chemical structure:

A. CATECHOLAMINES

1) NATURAL

1. Epinephrine
2. Nor epinephrine
3. Dopamine

2) synthetic

1. Dobutamine
2. Isoproterenol

B. NON-CATECHOLAMINES:

1. Phenylephrine
2. Ephedrine
3. Amphetamines
4. Dexamphetamine
5. Hydroxyamphetamine
6. Methylamphetamine
7. Metaproterenol
8. Salbutamol
9. Terbutaline
10. Methoxamine
11. Phenylpropanolamine
12. Naphazoline

Catecholamines: These compounds share the following properties:

■ **1. High potency**

■ **2. Rapid inactivation:** Catecholamines are metabolized by **COMT** postsynaptically & by **MAO** intraneuronally as well as by COMT & MAO in the gut wall & by MAO in the liver. Thus, catecholamines have only a brief period of action when given parenterally & they are inactivated (ineffective) when administered orally. **Short $T_{1/2}$.**

■ **3. Poor penetration into the CNS:**

Catecholamines are polar & therefore do not

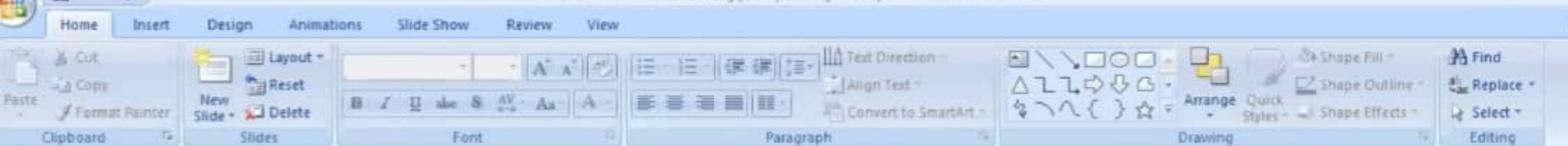
readily penetrate into the CNS. Nevertheless, most catecholamines have some clinical effects (**anxiety, tremor & headaches**) that are attributable to action on the CNS.

■ Noncatecholamines:

1. Compounds lacking the catechol hydroxyl groups have longer $t_{1/2}$ because they are not inactivated by **COMT**. These agents are poor substrates for MAO & thus show a **prolonged duration of action**.

2. **Increased lipid solubility** of many of the noncatecholamines (due to lack of polar OH groups) permits greater access to CNS.

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Outline

ready products like CHL. Reversible, most catecholamines have the direct effect on α₁ and α₂ receptors. But are irreversible to act on the CHL.

Noncatecholamines:

1. Compounds lacking the catechol hydroxyl groups have longer t_{1/2} because they are not metabolized by COMT. These agents are just substrates for MAO-B that shows prolonged action. (e.g. 20h)
2. Increased lipophilicity of many of the noncatecholamines due to lack of polar OH groups permits greater access to CHL.

According to mechanism of action:

A. DIRECTLY ACTING ON ADRENERGIC RECEPTORS: (they directly interact with & activate adrenoceptors)

1. Epinephrine	9. Dopamine
2. Nor epinephrine	10. Ritodrine
3. Dobutamine	
4. Terbutaline	
5. Isoproterenol	
6. Salbutamol	
7. Phenylephrine	
8. Methoxamine	

B. INDIRECT ACTING: May have either of 2 different mechanisms:

- 1) displacement of stored catecholamines from adrenergic stores making e.g. tyramine.
- 2) inhibition of synthesis of already released catecholamines. e.g. cocaine & Metyrosine (metyrosine, Reserpine, Reserpamine, Doxamine).

Sympathomimetic drugs acting indirectly are:

1. Amphetamines
2. Metamphetamines
3. Phenylethylamine
4. Tyramine
5. Methylphenidate
6. Moxidone

C. Monoamines:

Directly & indirectly acting adrenergic catecholamines:

1. Phenylephrine

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Outline

readily penetrates the CNS. Neurotoxic. Most catecholamines have the clinical effects of amphetamines. Amphetamines are amphetamine to act on the CNS.

Neurotoxicity:

1. Compounds lacking the catechol moiety group have higher toxicity because they are not metabolized by COMT. These agents are poor substrates for MAO & thus show a prolonged action. (e.g. 2,3-DMA)
2. Increased toxicity of many of the norepinephrine due to lack of catechol group: prevents greater access to CNS.

Amphetamines: mechanism of action:

1. Displacement of stored catecholamines from adrenergic nerve ending
2. Inhibition of reuptake of already released catecholamines

Amphetamines:

1. Amphetamine
2. Methamphetamine
3. Propylhexamine
4. Fenproporex
5. Mazindol
6. Mefenorex
7. Mefenorex
8. Mefenorex
9. Mefenorex
10. Mefenorex

B. INDIRECT ACTING: May have either of 2 different mechanisms:

- 1) displacement of stored catecholamines from adrenergic nerve ending e.g. tyramine.
- 2) inhibition of reuptake of already released catecholamines e.g. cocaine & tricyclic antidepressant, Atomoxetine, Reboxetine, Sibutramine, Duloxetine.

Sympathomimetic drugs acting indirectly are:

1. Amphetamine
2. Methamphetamine
3. Phenylephrine
4. Tyramine
5. Methylphenidate
6. Moxidipine

C. Monoamines:

Disrupt & indirectly by releasing catecholamines:

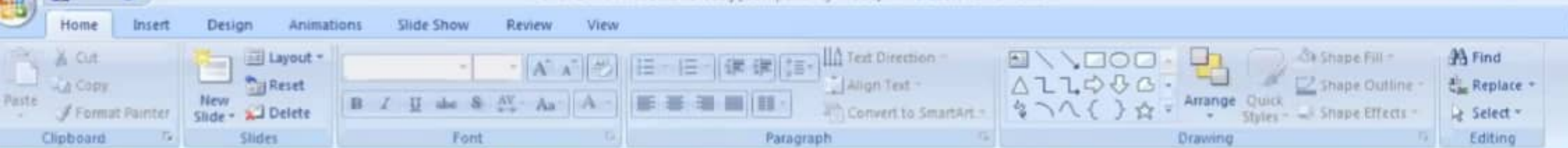
1. Phenylephrine

B. INDIRECT ACTING: May have either of 2 different mechanisms:

1) displacement of stored catecholamines from adrenergic nerve ending e.g. tyramine.

2) inhibition of reuptake of already released catecholamines e.g. cocaine & tricyclic antidepressant, Atomoxetine, Reboxetine, Sibutramine, Duloxetine.

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Slides Outline

- 1. MIXED ACTIVITY :
Directly & indirectly by releasing catecholamines :
1. Phenylpropanolamine
2. Ephedrine
3. Pseudo-ephedrine
- 2. ACTING ON ALPHA RECEPTORS :
1. Methoxamine
2. Phenylephrine
3. Midodrine
- 3. ACTING ON BETA RECEPTORS :
1. Dobutamine
2. Prenalolol
3. Terbutaline

C. MIXED ACTIVITY :
(Directly & indirectly by releasing catecholamines):

1. Phenylpropanolamine
2. Ephedrine
3. Pseudo-ephedrine

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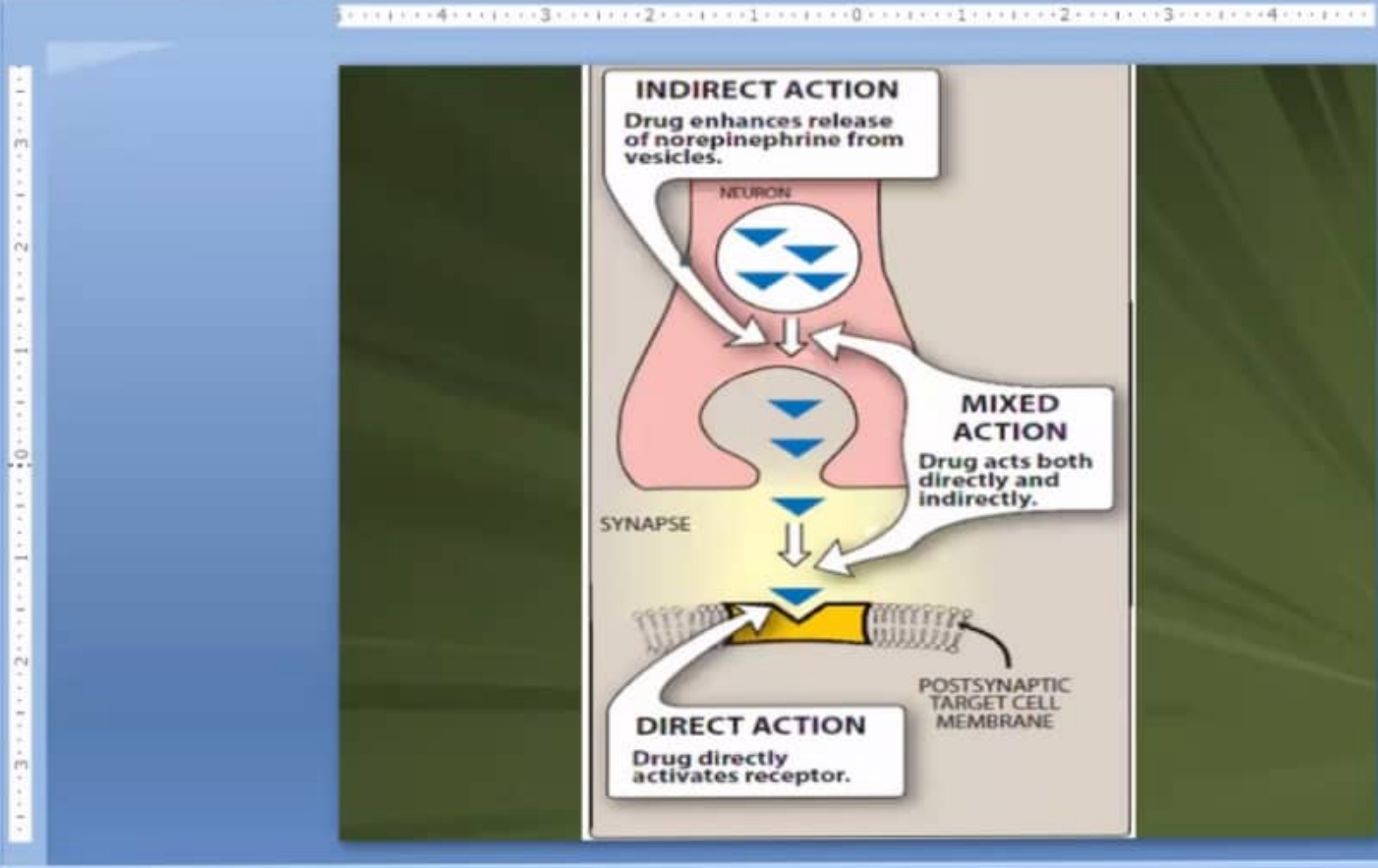
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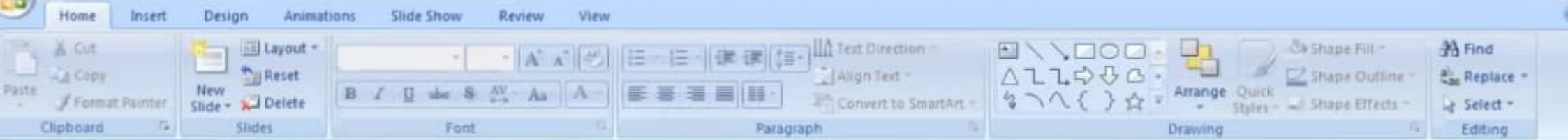
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Slides Outline

- Sympathomimetic drugs acting indirectly are:
 1. Amphetamine
 2. Methamphetamine
 3. Pseudoephedrine
 4. Tyramine
 5. Methylphenidate
 6. Modafinil
- MIXED ACTIVITY: Drugs & indirectly act on both adrenergic receptors!
 1. Phenylephrine
 2. Ephedrine
 3. Pseudoephedrine
- ACTING ON ALPHA RECEPTORS:
 1. Methoxamine
 2. Phenylephrine
 3. Midodrine
- Alpha 2 selective:
 1. Clonidine
 2. Medetomidine
 3. Apraclonidine
 4. Oxymetazoline
 5. Tizanidine



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Slides Outline

- 1. Sympathomimetic drugs acting indirectly are
 - 1. Amphetamine
 - 2. Methamphetamine
 - 3. Phenylephrine
 - 4. Tyramine
 - 5. Methylphenidate
 - 6. Mocaine
- 2. **Direct Activity:**
Effects & Indirectly on receptors
 - 1. Phenylephrine
 - 2. Ephedrine
 - 3. Pseudo-ephedrine
- 3.
- 4. **Actions on receptors:**
 - A. **ACTING ON ALPHA RECEPTORS:**
 - i. **Alpha-1 selective (agonist) (Relatively):**
 - 1. Methoxamine
 - 2. Phenylephrine
 - 3. Midodrine
- 5. **Alpha-2 selective (Relatively):**
 - 1. Clonidine
 - 2. Methyldine
 - 3. Apraclonidine
 - 4. Oxymetazoline
 - 5. Tetracaine

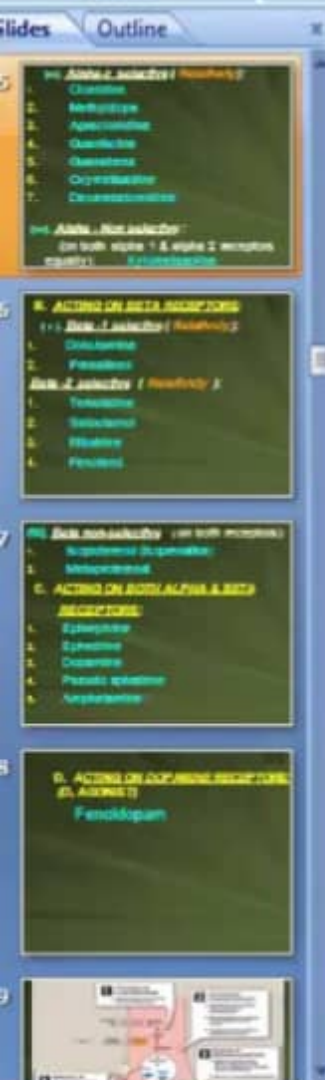
III. According to receptor-selectivity:

A. ACTING ON ALPHA RECEPTORS:

i. Alpha-1 selective (agonist) (Relatively):

- Methoxamine
- Phenylephrine
- Midodrine

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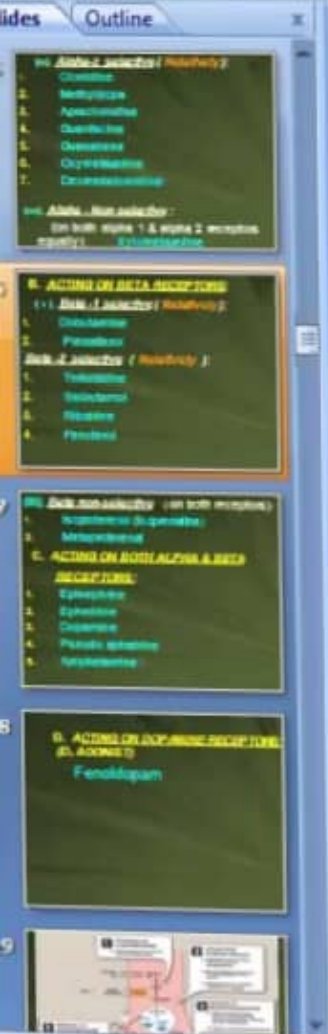
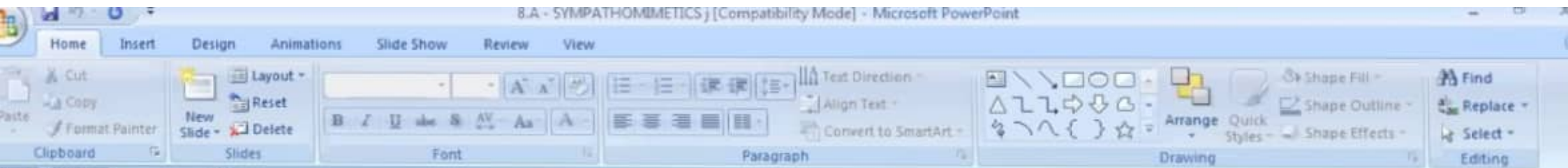
(ii). Alpha-2 selective (**Relatively**):

1. Clonidine
2. Methyldopa
3. Apraclonidine
4. Guanfacine
5. Guanabenz
6. Oxymetazoline
7. Dexmedetomidine

(iii). Alpha - Non selective :

(on both alpha 1 & alpha 2 receptors equally): Xylometazoline

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B. ACTING ON BETA RECEPTORS:

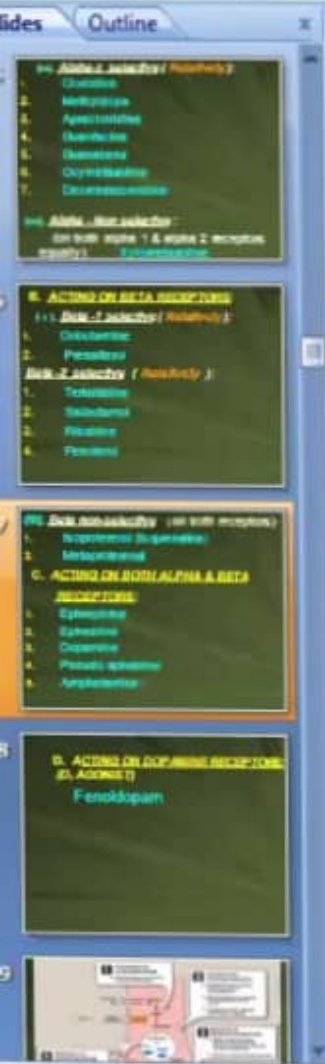
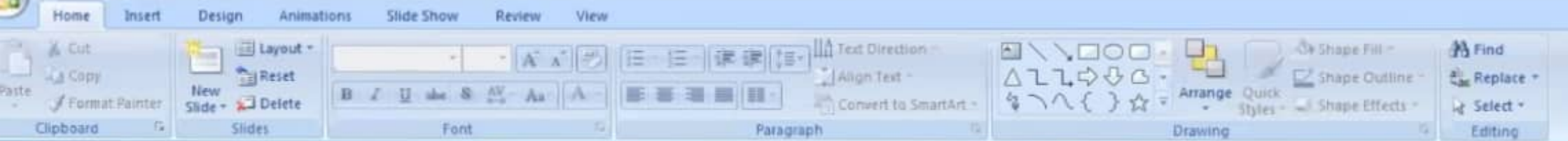
(i). Beta -1 selective (Relatively):

1. Dobutamine
2. Prenalterol

Beta -2 selective (Relatively):

1. Terbutaline
2. Salbutamol
3. Ritodrine
4. Fenoterol

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(iii). Beta non-selective (on both receptors):

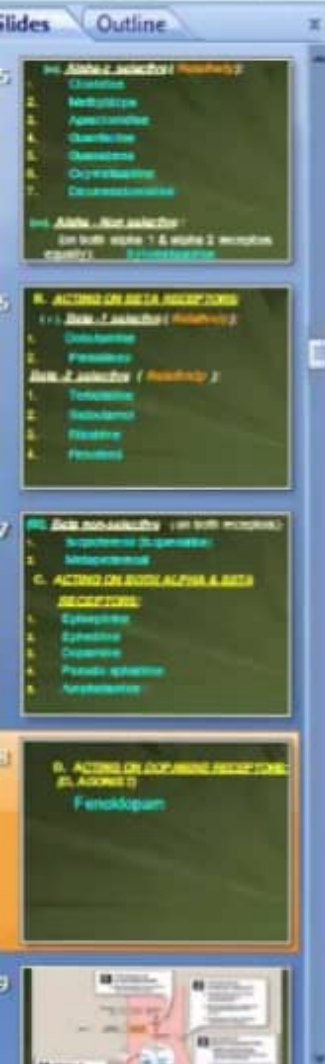
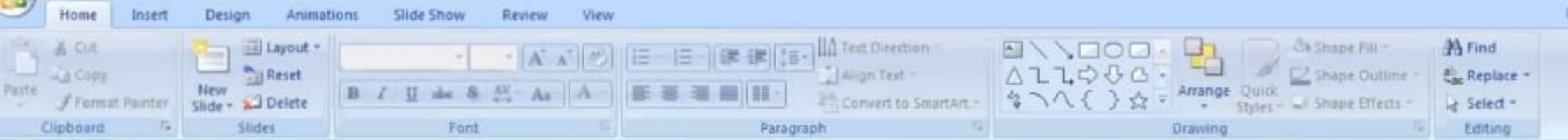
1. Isoproterenol (Isoprenaline)
2. Metaproterenol

C. ACTING ON BOTH ALPHA & BETA

RECEPTORS:

1. Epinephrine
2. Ephedrine
3. Dopamine
4. Pseudo ephedrine
5. Amphetamine

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4 3 2 1 0 1 2 3 4

3 2 1 0 1 2 3

D. ACTING ON DOPAMINE RECEPTORS:
(D₁ AGONIST)

Fenoldopam

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Slides Outline

PHARMACOLOGY: NE, SP1 & DOPAMINE readily metabolized by COMT & MAO. So inactive only & must be given parentally. Here's a bit of fun of action. They don't enter CNS in sufficient amounts even when given parentally. When released from nerve endings, they are subsequently taken up by NET & DAT into nerve endings & into postsynaptic cells. This uptake may also occur with NE, SP1, DOPAMINE given at high concentrations as evident in CNS. Adrenaline acts on adrenergic receptors, mainly alpha, mainly enter CNS & has effects like reach target. THYRAMINE is easily metabolized to SPH.

MOLECULAR PHARMACOLOGY UNDERSTANDING THE ACTIONS OF SYMPATHOMIMETIC DRUGS

The effects of catecholamines are mediated by cell-surface receptors. Adrenergic receptors are G-protein-coupled receptors (GPCRs). These receptors are coupled to G proteins that regulate various effector proteins. Each G protein is a heterotrimer consisting of α , β , and γ subunits. G proteins are classified on the basis of their distinctive β subunits. β subunits are classified into β_1 , β_2 , β_3 , β_4 , β_5 , β_6 , β_7 , β_8 , β_9 , β_{10} , β_{11} , β_{12} , β_{13} , β_{14} , β_{15} , β_{16} , β_{17} , β_{18} , β_{19} , β_{20} , β_{21} , β_{22} , β_{23} , β_{24} , β_{25} , β_{26} , β_{27} , β_{28} , β_{29} , β_{30} , β_{31} , β_{32} , β_{33} , β_{34} , β_{35} , β_{36} , β_{37} , β_{38} , β_{39} , β_{40} , β_{41} , β_{42} , β_{43} , β_{44} , β_{45} , β_{46} , β_{47} , β_{48} , β_{49} , β_{50} , β_{51} , β_{52} , β_{53} , β_{54} , β_{55} , β_{56} , β_{57} , β_{58} , β_{59} , β_{60} , β_{61} , β_{62} , β_{63} , β_{64} , β_{65} , β_{66} , β_{67} , β_{68} , β_{69} , β_{70} , β_{71} , β_{72} , β_{73} , β_{74} , β_{75} , β_{76} , β_{77} , β_{78} , β_{79} , β_{80} , β_{81} , β_{82} , β_{83} , β_{84} , β_{85} , β_{86} , β_{87} , β_{88} , β_{89} , β_{90} , β_{91} , β_{92} , β_{93} , β_{94} , β_{95} , β_{96} , β_{97} , β_{98} , β_{99} , β_{100} .

β_1 , stimulates G protein of adenyl cyclase.

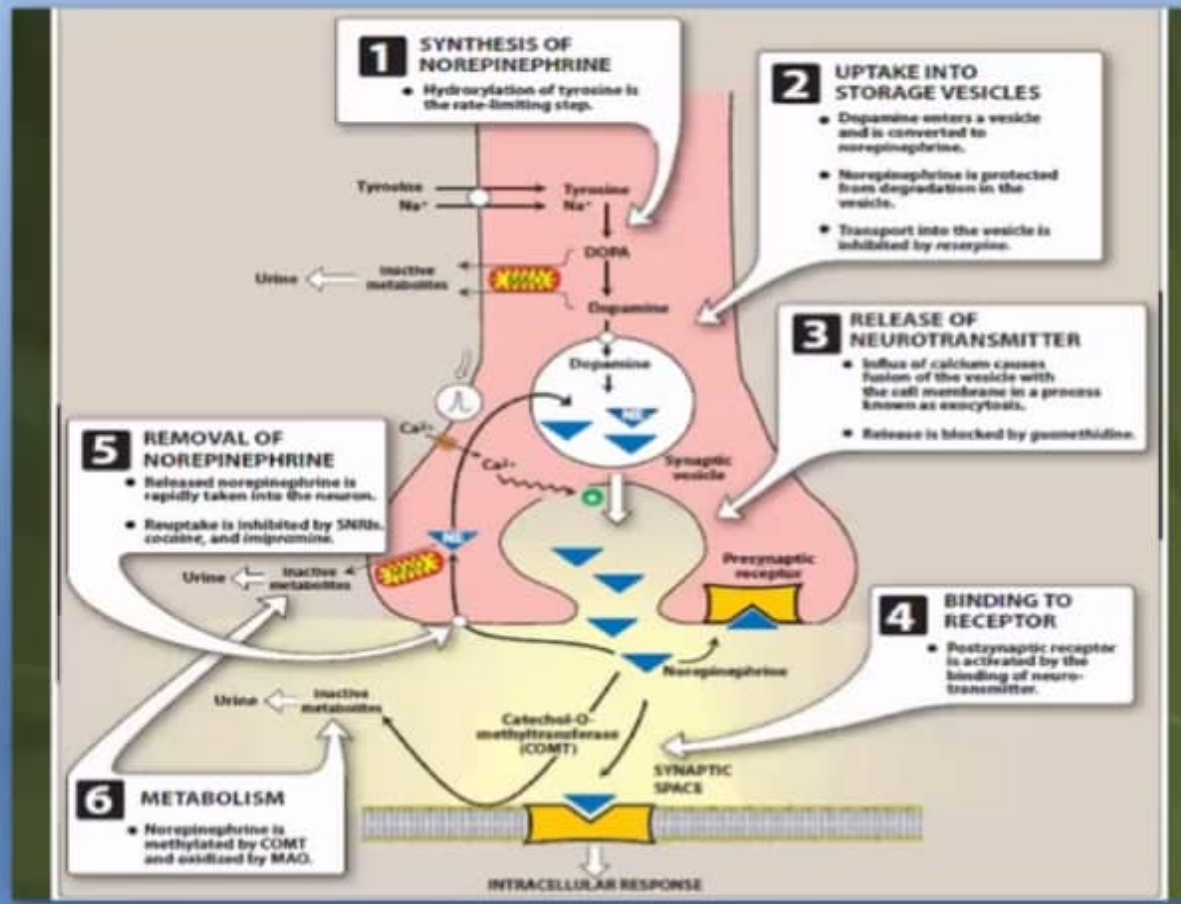
β_2 and β_3 , the inhibitory G proteins of adenyl cyclase and

β_4 and β_{11} , the G proteins coupling β receptors to phospholipase C.

The activation of G protein-coupled receptors by catecholamines provides the dissociation of guanine diphosphate (GDP) from the β subunit of G protein. Guanine nucleotide (GTP) then binds to β_1 , β_2 , β_3 , β_4 , β_{11} , β_{12} , β_{13} , β_{14} , β_{15} , β_{16} , β_{17} , β_{18} , β_{19} , β_{20} , β_{21} , β_{22} , β_{23} , β_{24} , β_{25} , β_{26} , β_{27} , β_{28} , β_{29} , β_{30} , β_{31} , β_{32} , β_{33} , β_{34} , β_{35} , β_{36} , β_{37} , β_{38} , β_{39} , β_{40} , β_{41} , β_{42} , β_{43} , β_{44} , β_{45} , β_{46} , β_{47} , β_{48} , β_{49} , β_{50} , β_{51} , β_{52} , β_{53} , β_{54} , β_{55} , β_{56} , β_{57} , β_{58} , β_{59} , β_{60} , β_{61} , β_{62} , β_{63} , β_{64} , β_{65} , β_{66} , β_{67} , β_{68} , β_{69} , β_{70} , β_{71} , β_{72} , β_{73} , β_{74} , β_{75} , β_{76} , β_{77} , β_{78} , β_{79} , β_{80} , β_{81} , β_{82} , β_{83} , β_{84} , β_{85} , β_{86} , β_{87} , β_{88} , β_{89} , β_{90} , β_{91} , β_{92} , β_{93} , β_{94} , β_{95} , β_{96} , β_{97} , β_{98} , β_{99} , β_{100} .

Has the β_1 cell. The activated GTP-bound β subunit then regulates the activity of its effector.

Effectors of adrenergic receptors activated β subunits include adenyl cyclase, cAMP, phospholipase C, phospholipase C and



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Slides Outline



PHARMAACOKINETICS: NE, EPI & DOPAMINE rapidly metabolized by COMT & MAO. So inactive orally & must be given parenterally. Have a short duration of action. They do not enter CNS in sufficient amounts even when given parenterally. When released from nerve endings, they are subsequently taken up by NET & DAT into nerve endings & into perisynaptic cells. This uptake may also occur with NE, EPI & DOPAMINE given as drugs. Amphetamines are resistant to MAOs, orally active, readily enter CNS & their effect lasts much longer. TYRAMINE is rapidly metabolized by MAOs.

MOLECULAR PHARMACOLOGY UNDERSTANDING THE ACTIONS OF SYMPATHOMIMETIC DRUGS

The effects of catecholamines are mediated by cell-surface receptors.

Adrenergic receptors are α and β adrenergic receptors (GPCRs). These receptors are coupled to G proteins that regulate various effector proteins. Each G protein is a heterotrimer consisting of α , β , and γ subunits. G proteins are classified on the basis of their distinctive β subunits. β_1 proteins (found in the heart) are associated with adenylyl cyclase.

β_2 , β_3 , and β_4 stimulate G protein of adenylyl cyclase.

β_1 and β_2 , the inhibitory G proteins of adenylyl cyclase are

β_3 and β_4 , the G proteins coupling β receptors to phospholipase C.

The activation of G protein-coupled receptors by catecholamines provides the dissociation of guanine diphosphate (GDP) from the β subunit of G protein. Guanine triphosphate (GTP) then binds to the α subunit, & a subsequent dissociation.

With the β_1 subunit, the activated GTP-bound β subunit then regulates the activity of its effector.


Effects of adrenergic receptor activated β subunits include adenylyl cyclase, cAMP, phospholipase C, phospholipase C and

PHARMAACOKINETICS: NE, EPI & DOPAMINE rapidly metabolized by **COMT & MAO**. So inactive orally & must be given parenterally. Have a short duration of action. They do not enter CNS in sufficient amounts even when given parenterally. When released from nerve endings, they are subsequently taken up by **NET & DAT** into nerve endings & into **perisynaptic cells**. This uptake may also occur with NE, EPI & DOPAMINE given as drugs. **Amphetamines** are resistant to **MAOs**, orally active, readily enter **CNS** & their effect lasts much longer. **TYRAMINE** is rapidly metabolized by MAOs.

Click to add notes



Slides Outline



PHARMACOLOGY OF NE, SPH & DOPAMINE
 NE, SPH & DOPAMINE are synthesized by COMT & MAO. NE, SPH & DOPAMINE are not reabsorbed into the presynaptic terminal. NE, SPH & DOPAMINE are metabolized by COMT & MAO. NE, SPH & DOPAMINE are metabolized by COMT & MAO.

MOLECULAR PHARMACOLOGY UNDERLYING THE ACTIONS OF SYMPATHOMIMETIC DRUGS
 The effects of catecholamines are mediated by cell-surface receptors. Adrenoceptors are coupled to G proteins that regulate various effector proteins. Each G protein is a heterotrimer consisting of α , β , and γ subunits. G proteins are classified on the basis of their distinctive β subunits. G proteins of particular importance for adrenoceptor function include:

- G_s , stimulates G protein of adenyl cyclase.
- G_i and G_o , the inhibitory G proteins of adenyl cyclase and
- G_{12} and G_{13} , the G proteins coupling to phospholipase C.

The activation of G protein-coupled receptors by catecholamines provides the dissociation of guanine diphosphate (GDP) from the β subunit of G protein. Guanine diphosphate (GDP) then binds to β , γ , and α subunits.

Then the β subunit, the activated GTP-bound β subunit, then regulates the activity of its effector.

Effects of adrenoceptor activated β subunits include adenyl cyclase, cAMP, phospholipase C, phospholipase C and

MOLECULAR PHARMACOLOGY UNDERLYING THE ACTIONS OF SYMPATHOMIMETIC DRUGS

The effects of catecholamines are mediated by cell-surface receptors.

Adrenoceptors are typical G protein-coupled receptors (GPCRs). These receptors are coupled to G proteins that regulate various effector proteins. Each G protein is a heterotrimer consisting of α , β , and γ subunits.

G proteins are classified on the basis of their distinctive β subunits. G proteins of particular importance for adrenoceptor function include

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Slides Outline

PHARMACOLOGY: NE, SPH & DOPAMINE mostly released by CBMT & MAO. So inactive only & must be given parentally. Have a short duration of action. They do not enter CNS in sufficient amounts even when given parentally. When released from nerve endings, they are subsequently broken up by MAO & COMT into metabolites & into amine precursors. This action may also occur with NE, SPH, DOPAMINE given as drugs. **Amphetamine** an indirect sympathomimetic, mainly enter CNS & has effect both reach target. **THYRAMINE** is easily metabolized to SPH.

MOLECULAR PHARMACOLOGY UNDERSTANDING THE ACTIONS OF SYMPATHOMIMETIC DRUGS
The effects of catecholamines are mediated by cell-surface receptors.
Adrenergic receptors are G-protein-coupled receptors (GPCRs). These receptors are coupled to G proteins that regulate various effector proteins. Each G protein is a heterotrimer consisting of α , β , and γ subunits. G proteins are classified on the basis of their distinctive β subunits. **α subunits** - **Major role** - **Implicated in intracellular signaling**.

- G_s , stimulatory G protein of adenylyl cyclase.**
- G_i and G_o , the inhibitory G proteins of adenylyl cyclase and**
- G_q and G_{11} , the G proteins coupling β receptors to phospholipase C.**
- The activation of G protein-coupled receptors by catecholamines promotes the dissociation of guanosine diphosphate (GDP) from the β subunit of G protein. **Guanosine triphosphate (GTP)** then binds to the α subunit & α subunit dissociates.
- With the $\beta\gamma$ unit. The activated GTP-bound β subunit then regulates the activity of its effector.
- Effects of adrenergic activated α subunits include adenylyl cyclase, cAMP, phospholipase C, phospholipase C and

- **G_s , stimulatory G protein of adenylyl cyclase,**
- **G_i and G_o , the inhibitory G proteins of adenylyl cyclase and**
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- The activation of G protein-coupled receptors by catecholamines promotes the dissociation of guanosine diphosphate (GDP) from the β subunit of G protein. **Guanosine triphosphate (GTP)** then binds to this G protein & α subunit dissociates

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Beta - 1 receptors: (Stimulatory)

Heart: *Increases rate & force of contraction*

Juxtaglomerular cells: *Increases renin release*

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Slides Outline

1. **How the drug acts.** The activated GTP-bound α_1 receptor then regulates the activity of its effector.

2. **Effects of adrenoceptor activated a subunit include activity of cyclase, cAMP, phospholipase C, phospholipase C and ion channels.**

3. **The α_1 subunit is linked to the activation of the enzyme IP₃ or DAG and phospholipase C, and the subsequent activation of PKC.**

4. **Mechanism of action of adrenoceptor agonists:**

1. **Direct-acting agonists:** These drugs act directly on α or β receptors producing effect similar to those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal.

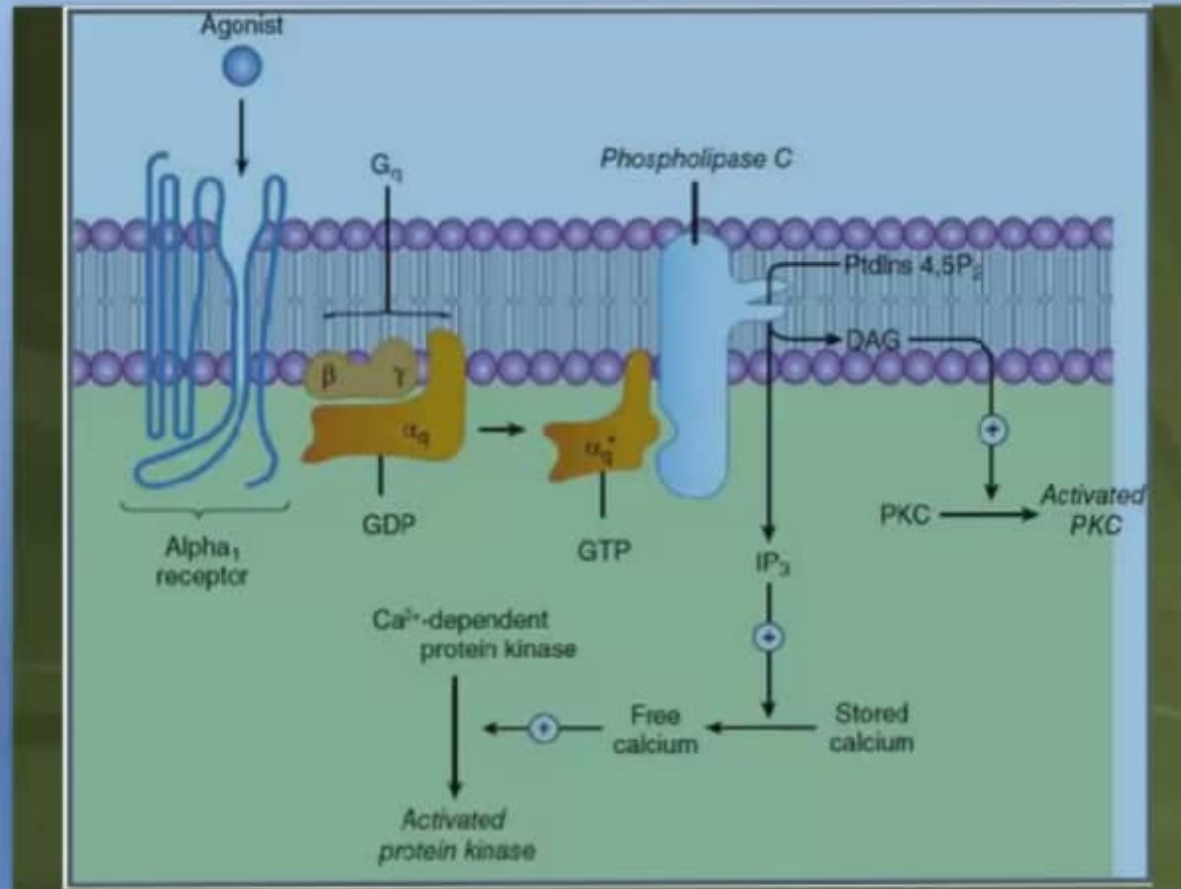
2. **Indirect-acting agonists:** These agents may block the reuptake of NE or cause the release of NE from the cytoplasmic vesicle or vesicles of the adrenergic neuron. NE then binds to the α and β receptors and acts to activate PKC. Examples of indirect agonists & agents that cause NE release include cocaine and amphetamine respectively.

5. **Block-acting agonists:** Ephedrine and its stereoisomer, pseudoephedrine both stimulate adrenergic activity and mirror sympathomimetic from the adrenergic neuron.

6. **SYMPATHOMIMETICS**

Activation of α_1 receptors leads to α_1 activation, which is coupled to G_q, to phospholipase C. This enzyme produces diacylglycerol (DAG) and inositol trisphosphate (IP₃).

7. IP₃ promotes release of Ca²⁺ from the ER.



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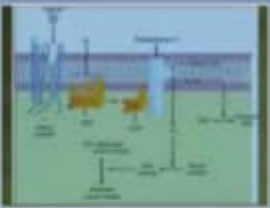


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From the β₁ cell, the activated GTP-bound α subunit then activates the activity of its effector.

1. Effects of adrenoceptor activated α subunits include adenylyl cyclase, Ca²⁺ phospholipase C and ion channels.

2. The α subunit is inactivated by hydrolysis of the bound GTP to GDP and phosphate, and the subsequent re-association of the α subunit with the β₁.



Mechanism of action of adrenergic agonists

1. **Direct-acting agonists:** These drugs act directly on α or β receptors producing effects similar to those that occur following stimulation of sympathetic nerves or release of norepinephrine from the adrenal.

2. **Indirect-acting agonists:** These agonists may block the reuptake of NE or cause the release of NE from the cytoplasmic pool or vesicles of the adrenergic neuron. NE then interacts with α-receptors and leads to α₁ or β₁ receptors. Examples of indirect-acting α₁ agonists that cause NE release include cocaine.

and amphetamines respectively

3. **Mixed-action agonists:** Ephedrine and its stereoisomer, pseudoephedrine both stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron.

PHARMACODYNAMICS

Activation of α₁ receptors leads to:

1. α₁ receptors are coupled to G_q to phospholipase C. This enzyme produces inositol trisphosphate and leads to formation of IP₃ & Ca²⁺.

2. IP₃ promotes release of Ca²⁺ from the sarcoplasmic reticulum.

and amphetamines respectively.

3. Mixed-action agonists: Ephedrine and its stereoisomer, pseudoephedrine both stimulate adrenoceptors directly and release norepinephrine from the adrenergic neuron.

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Slides Outline

1. Mechanism of action of adrenergic agonists

2. and adrenergic receptors

3. PHARMACODYNAMICS

4. DAG activates Protein Kinase C which phosphorylates its other primary signaling pathway.

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PHARMACODYNAMICS:

Activation of α_1 receptors leads to

- α_1 receptors are coupled via G_q to phospholipase C. This enzyme hydrolyses polyphosphoinositides and leads to formation of IP_3 & DAG.
- IP_3 promotes release of sequestered Ca^{++} from I/C stores & thus \uparrow the cytoplasmic concentration of free Ca^{++} & activation of Ca^{++} dependent protein kinases which phosphorylate their substrate.

IP_3 is subsequently dephosphorylated which ultimately leads to formation of free INOSITOL.

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Outline

1. **Direct-acting agonists.** These drugs act directly on a or β receptors causing effects similar to those that occur following liberation of neurotransmitter or release of substance from the nerve.

2. **Indirect-acting agonists.** These agonists increase the release of NE or cause the release of NE from the sympathetic nerve or inhibit of NE reuptake neurons. All these agonists are competitive with NE and NE receptors. Examples include tyramine. Agents that block NE release include cocaine.

and adrenergic receptors

3. **Block-acting agonists.** Sympathomimetics that stimulate adrenergic activity and cause sympathomimetic effects on the adrenergic system.

PHARMACODYNAMICS

Activation of β_1 -receptors leads to

1. a. increase in heart rate (HR) in chronotropic response. This response is mediated by activation of SA node.
2. b. increase in force of contraction (CO) in inotropic response. This is the response of the heart to increased HR and is mediated by activation of SA node which increases the force of contraction.

It is also important to understand that activation leads to dilation of the blood vessels.

3. **CO2 activates Protein Kinase C which modulates activities of many signaling pathways.**

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Slides Outline

PROPRIOCEPTIVE
Activation of G_i receptors leads to:
1. G_i receptors are coupled to G_i to phospholipase C. This enzyme produces $inositol(1,4,5)P_3$ and leads to formation of IP_3 & DAG
2. IP_3 promotes release of sequestered Ca^{2+} from its stores. & thus Ca^{2+} the (cyclic) concentration of Ca^{2+} is, activation of Ca^{2+} dependent protein kinase which phosphorylates their substrate.
 IP_3 is subsequently phosphorylated which ultimately leads to formation of the IP_4 .

1. DAG activates Phospholipase C which produces additional of IP_3 leading to IP_4 .

Activation of β_2 receptors leads to:
1. Inhibition of adenylyl cyclase activity mediated by inhibitory G_i & causes decrease in intracellular cAMP levels.
2. β_2 receptors use other signalling pathways, involving regulation of activities of ion-channels & activities of imp. enzymes involved in signal transduction.
3. Some of the effects of β_2 receptors are independent of their ability to inhibit adenylyl cyclase e.g. β_2 - receptor agonists cause platelet aggregation & decrease in cAMP levels.

Further observations: The α_1 and α_2 receptors are further distinguished by α_1 , α_1C , and α_1D receptors (in α_1), and α_2A , α_2B , and α_2C . This extensive classification is necessary for understanding the selectivity of drugs by agonists & a selective α_1A antagonist that is used to treat benign prostatic hyperplasia.
The drug α_1 antagonist is used because it blocks α_1A receptors. Some α_1 receptors in the vasculature are coupled to Ca^{2+} release from the sarcoplasmic reticulum in the blood vessels.

BETA RECEPTORS Activation of β_2 receptors results in stimulation of adenylyl cyclase & inc. conversion of ATP into cAMP. This is mediated by G_s .
1. cAMP is a 2^{nd} messenger of β receptor activation e.g. in liver β receptors, β receptor activates cAMP synthesis leads to

Activation of : α_2 - receptors leads to:

1. inhibition of adenylyl cyclase activity transduced by inhibitory G_i & causes decrease in intracellular cAMP levels.
2. α_2 - receptors use other signalling pathways, including regulation of activities of ion-channels & activities of imp. enzymes involved in signal transduction.
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Slides Outline

1. Adrenergic receptors leads to

1. α_1 receptors are coupled to G_q to phospholipase C. This enzyme cleaves phospholipids and leads to formation of DAG & IP₃.
2. IP₃ promotes release of sequestered Ca²⁺ from ER stores & thus ↑ the cytosolic concentration of free Ca²⁺ & activation of Ca²⁺ dependent protein kinases which phosphorylate their substrate.
3. IP₃ & subsequently diacylglycerol which ultimately leads to formation of the PKC/PLA₂.

2. DAG activates Protein Kinase C which modulates activities of many signaling pathways.

Adrenergic receptors leads to

1. inhibition of adenylate cyclase activity mediated by inhibitory G_i causes decrease in intracellular cAMP levels.
2. β_1 receptors use other signaling pathways, involving activation of adenylyl cyclase & activities of this enzyme and subsequent breakdown.
3. Some of the effects of β_1 receptors are independent of their ability to control adenylyl cyclase e.g. β_1 receptor agonists cause platelet aggregation & stimulate cAMP levels.

Further subdivisions. The α_1 and α_2 receptors are further subdivided into α_{1A} , α_{1B} , α_{1C} , and α_{1D} and into α_{2A} , α_{2B} , and α_{2C} . This extended classification is necessary for understanding the selectivity of some drugs eg tamsulosin is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia.

The drug has fewer CV side effects because it targets α_{1A} subtype receptors found primarily in the urinary tract and prostate gland and does not affect the α_{1B} subtype found in the blood vessels.

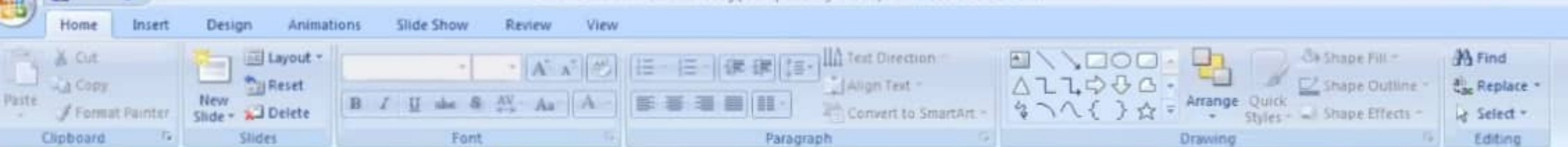
β_2 receptors. Activation of β_2 receptors results in stimulation of adenylyl cyclase & inc. conversion of ATP into cAMP. This is mediated by G_s.

cAMP is the 2nd messenger of β receptor activation e.g. in liver primary cAMP & increases activation of PKA synthesis leads to

Further subdivisions: The α_1 and α_2 receptors are further divided into α_{1A} , α_{1B} , α_{1C} , and α_{1D} and into α_{2A} , α_{2B} , and α_{2C} . This extended classification is necessary for understanding the selectivity of some drugs eg *tamsulosin* is a selective α_{1A} antagonist that is used to treat benign prostatic hyperplasia.

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Slides Outline

- BETA RECEPTORS:** Activation of all 3 β receptors results in stimulation of adenylyl cyclase & inc. conversion of ATP into cAMP. This is mediated by Gs.
- cAMP is major 2nd messenger of β receptor activation e.g. in liver of many species, β receptor activated cAMP synthesis leads to a cascade of events culminating in inactivation of glycogen phosphorylase.
- In heart, β receptor activated cAMP synthesis \uparrow flux of Ca^{++} across the cell membrane & its sequestration inside the cell.
- β receptor activation also provides stimulation of the Adenylylation of the effect & increases. It may involve phosphorylation of MLCK via feedback loop.
- β receptor may activate collagenase. Ca increases in heart, so Ca release enhancement independently of changes in cAMP conc.
- Under certain circumstances, β receptor may couple to Gq which has been shown to activate phospholipase C (phospholipase C).
- Dopamine Receptors:**
- D1 receptors: typically associated with stimulation of adenylyl cyclase which leads to accumulation of cAMP.
- D₂ receptor induced β activation is primarily due to accumulation of cAMP in the striatum. Receptors of brain vascular beds in which dopamine is a vasodilator.
- D4 receptors: associated with inhibition of adenylyl cyclase leading to opening of potassium channels & decrease in heart rate.
- Respiratory Regulation & Polyspermatid**
- Respiratory CTR of adenylylation are changing all the time and being regulated by catecholamines, thyroid hormones, vitamin C, and Wago, age & stress factors.
- One of the best known examples of receptor regulation is desensitization of adenylylation that may occur after exposure to catecholamines & other sympathomimetic drugs.
- After a cell has been exposed for a period of time to an agonist, that agonist often becomes less responsive to further stimulation by that agent. Other forms used to denote desensitization are tolerance, tachyphylaxis & tachyphylaxis.
- Receptor mechanisms contribute to desensitization. Some have fast and some slow.

- **BETA RECEPTORS** Activation of all 3 β receptors results in stimulation of adenylyl cyclase & inc. conversion of ATP into cAMP. This is mediated by Gs.
- cAMP is major 2nd messenger of β receptor activation e.g. in liver of many species, β receptor activated cAMP synthesis leads to a cascade of events culminating in inactivation of glycogen phosphorylase.
- In heart, β receptor activated cAMP synthesis \uparrow flux of Ca^{++} across the cell membrane & its sequestration inside the cell.

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BA - STRIPATHONAM (PLS) [Compatibility Mode] - Microsoft PowerPoint

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Outline

- 1. Activation of β_1 receptors leads to:
 1. Activation of β_1 receptors leads to increased cAMP levels which increases protein kinase A (PKA) activity.
 2. PKA then phosphorylates various proteins, including regulation of activities of myosin, leading to relaxation of smooth muscle.
 3. Some other effects of PKA are relaxation of heart muscle by several pathways e.g. by phosphorylation of calcium channels & activation of potassium channels.
- Further substrates: The set of substrates are different in different cells, e.g. PKA and PKC activate GSK-3 β , which inhibits β -catenin. This pathway is important for maintaining the stability of β -catenin. In a resting cell, β -catenin is bound to a protein complex, and it is only when this complex is degraded that β -catenin is free to act as a transcription factor.
- PKA also phosphorylates the β -adrenergic receptor, leading to its internalization and degradation. This is a feedback mechanism to prevent overstimulation of the receptor.
- PKA also phosphorylates the β -adrenergic receptor, leading to its internalization and degradation. This is a feedback mechanism to prevent overstimulation of the receptor.
- β receptor activation also promotes relaxation of SM. Although mechanism of SM effect is uncertain, it may involve phosphorylation of MLCK into inactive form.
- β receptor may activate voltage sensitive Ca channels in heart via Gs mediated enhancement independently of changes in cAMP conc.
- Under certain circumstances, β_2 receptors may couple to Gq which have been shown to activate MAP (mitogen activated protein) kinases.

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Slides Outline

Polymorphisms:
Genetic polymorphisms for many subtypes of α_1 , α_2 , and β so changing the susceptibility to diseases like heart failure, bronchial asthma.

ORGAN SYSTEM EFFECTS OF SYMPATHOMIMETICS

1. EFFECTS OF α_1 RECEPTOR ACTIVATION
 α_1 receptors widely distributed in smooth & skeletal muscle. Activation leads to vasoconstriction. A mutation in α_1 gene (polymorphism) in PVT & some vascular disorders. In α_1 gene, certain mutation leads to a rise in BP. Rise in BP with normal CO reflects rise in peripheral resistance. CO will not rise, since no vasoconstriction. CO will not rise, since no vasoconstriction. CO will not rise, since no vasoconstriction.

2. There are major differences in vascular response to α_1 stimulation in different individuals.

3. α_1 receptors have a receptor & variant 2 responses to NE & EP as are specified by 28, muscle fiber contractile force depending on number of α_1 receptors.

4. EFFECTS OF α_2 RECEPTOR ACTIVATION
 α_2 receptors are present in SV & their activation leads to vasoconstriction. This effect is observed only when α_1 receptors are given locally (near artery) & by IV. When given orally, they accumulate in CNS & their vasoconstrictor effects are outweighed by central effects of α_2 receptors which lead to inhibition of sympathetic tone & BP. So they are used in treatment of hypertension.

5. EFFECTS OF β RECEPTOR ACTIVATION
Stimulation of β receptors in heart \uparrow CO by stimulating contractility & by relaxation of SA node to \uparrow heart rate. It gives rise to PVT by activating β_1 receptors leading to \uparrow release of cardiac renin. This effect is to maintain or slightly inc. systolic BP & to inc. diastolic BP. Other effects include an increased output to SV receptors. β receptor activation leads to \uparrow CO & \downarrow in cardiac output. Pacemaker activity \uparrow \uparrow in β_1 receptors. Conduction velocity \uparrow in β_1 receptors. Inotropic effect & inotropic effect \uparrow in β_1 receptors. Rate of conduction & force of contraction \uparrow in β_1 receptors.

6. In the presence of some effects such as, direct effects on heart rate may be determined by a reflex response to BP. Physiological stimulation of heart by catecholamines leads to inc. coronary blood flow.

7. EFFECTS OF COMBINED RECEPTOR

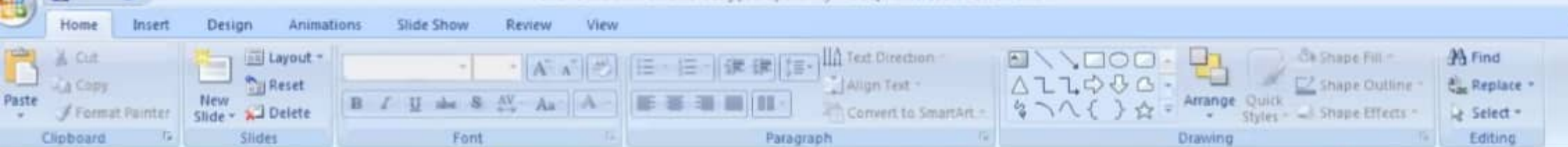
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3 2 1 0 1 2 3 4

Polymorphisms:

Genetic polymorphisms for many subtypes of α_1 , α_2 , and β so changing the susceptibility to diseases like heart failure, bronchial asthma.

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Slides Outline

Mechanism of Desensitization
A beta receptor desensitization and recovery results from phosphorylation of receptors by members of G protein coupled receptor kinase family of which there are 7 members. Some DR receptors become susceptible for this change only when they are bound to an agonist. It is an example of homologous desensitization since it involves only agonist coupled receptors. Phosphorylation of these receptors enhances their affinity for β agonist, a family of widely expressed proteins.

Upon binding of β agonist molecule, capacity of receptor to activate G proteins is limited. Available transmembrane with cytoskeleton Adaptor AP2, leading to endocytosis of receptors. Receptor desensitization may also be mediated by nerve messenger sodium. β receptors stimulate cAMP accumulation which leads to activation of protein kinase C which can phosphorylate residues on β receptors resulting in inactivation of receptor functions. (Heterologous Desensitization)

Polysymptomatic
Genetic polysymptomatic to many subtypes of α_1 , α_2 and β as changing the susceptibility to observe the heart failure, bronchial asthma.

ORGAN SYSTEM EFFECTS OF SYMPATHOMIMETICS
1. **EFFECTS OF α_1 RECEPTOR ACTIVATION:** α_1 receptors widely expressed in vessels & their activation leads to arterial & venoconstriction. A relatively pure α_1 agonist (phenylephrine) inc. PVR & dec. venous capacitance. So inc. arterial resistance leads to a rise in BP. This rise in BP with normal CV reflexes elicits a baroreceptor mediated inc. in vagal tone with slowing of heart rate. CO will not dec. since inc. venous return may inc. stroke volume.
2. There are major differences in receptor types expressed in various vascular beds. Skin BV

previously have α receptors & conduct a response to NE & EPI so we selective DR. DR, muscle DR may conduct a minor depending conditions if β are activated.

EFFECTS OF α_1 RECEPTOR ACTIVATION
 α_1 are present in BV & their activation leads to vasoconstriction. This effect is observed only when

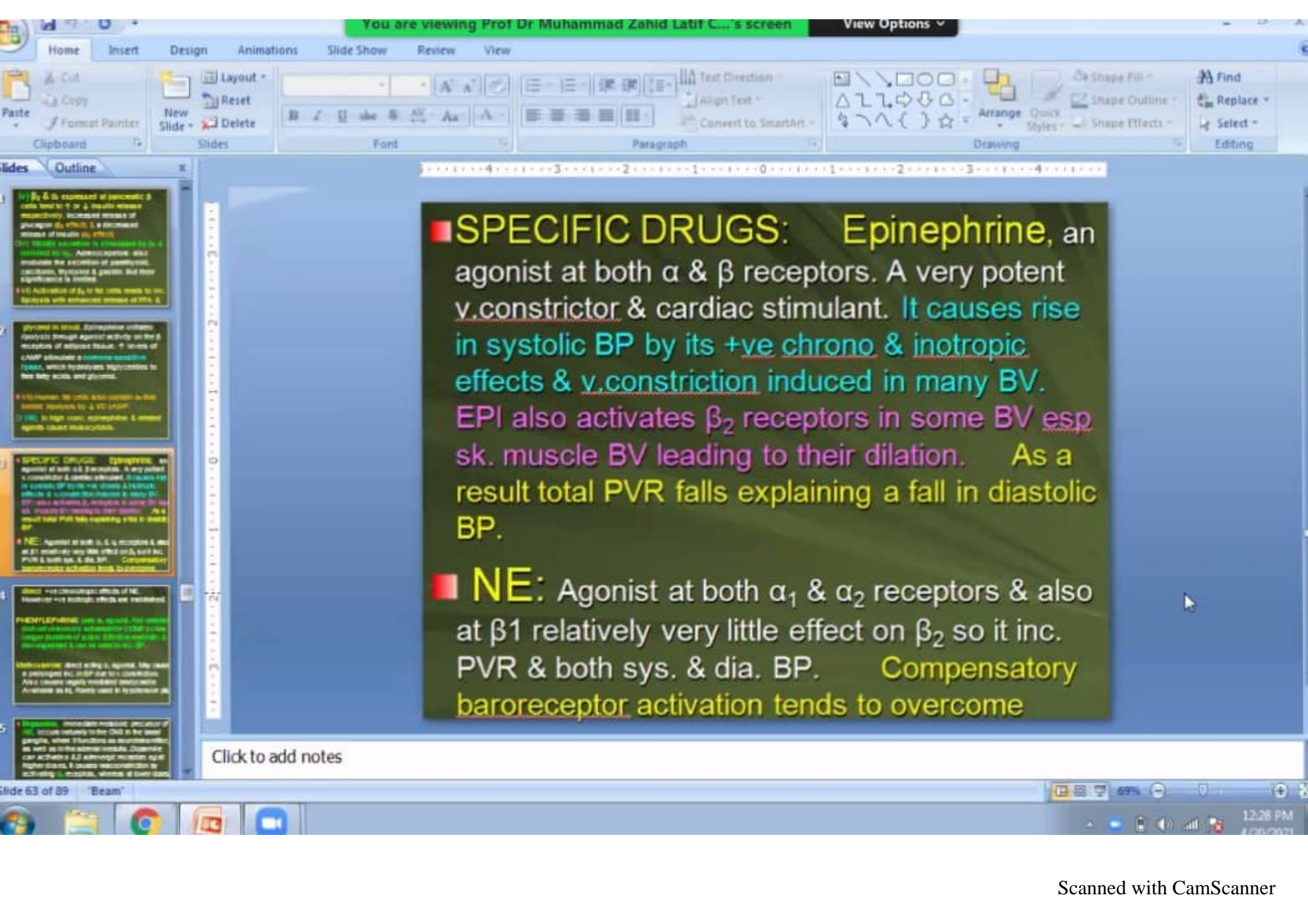
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- There are major differences in receptor types expressed in various vascular beds. Skin BV

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SPECIFIC DRUGS: **Epinephrine**, an agonist at both α & β receptors. A very potent v.constrictor & cardiac stimulant. **It causes rise in systolic BP by its +ve chrono & inotropic effects & v.constriction induced in many BV.** EPI also activates β_2 receptors in some **BV esp sk. muscle BV** leading to their dilation. As a result total **PVR** falls explaining a fall in diastolic BP.

NE: Agonist at both α_1 & α_2 receptors & also at β_1 relatively very little effect on β_2 so it inc. PVR & both sys. & dia. BP. **Compensatory baroreceptor activation tends to overcome**

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Outline pane showing slide content:

- 1) β_1 & β_2 are expressed at parasympathetic cells tend to \uparrow in β results increase respectively. Increased release of glucagon β_2 effect, a decreased release of insulin β_1 effect.
- 2) β_2 receptor activation is stimulated by β_2 is inhibited by α_2 . Adrenoreceptors also modulate the secretion of parathyroid, calcitonin, histamine & gastrin. But their significance is limited.
- 3) β_1 Activation of β_1 in fat cells leads to inc. lipolysis with enhanced release of FFA & glycerol in blood. Epinephrine inhibits lipolysis through agonist activity on the β receptors of adipose tissue. \uparrow levels of LAMP stimulate a hormone-sensitive lipase, which hydrolyzes triglycerides to free fatty acids and glycerol.
- 4) β_1 In heart, fat cells also contain β_1 but inhibit lipolysis to a β_2 extent.
- 5) β_2 In high conc. norepinephrine & epinephrine cause lipolysis.
- 6) **SPECIFIC DRUGS: Epinephrine**, an agonist at both α_1 & β receptors. A very potent vasoconstrictor & cardiac stimulant. Increases HR & contractility by β_1 inc. cAMP & contractile effect & vasoconstriction induced in very high dose. Also activates β_2 , inhibits β_1 and β_2 inc. lipolysis leading to free fatty acids. As a result total PVR falls resulting \uparrow flow to skeletal muscle.
- 7) **NE**: Agonist at both α_1 , α_2 , β_1 receptors & has β_1 activity very little effect on β_2 and β_2 PVR & both α_1 & β_2 SP. Compensatory sympathetic activation leads to increased PVR.
- 8) **Direct α_1 pharmacologic effects of NE**: However α_1 blockade effects are maintained.
- 9) **PHENYLEPHRINE** (an α_1 agonist) has similar pharmacologic activity to NE but is more potent. It has a longer duration of action. It is a vasoconstrictor & \uparrow in PVR. It is used in hypotensive pts.
- 10) **Methoxamine**: direct acting α_1 agonist. It causes a prolonged inc. in BP due to v. constriction. Also causes vagally mediated bradycardia. Available as inj. Rarely used in hypotensive pts.
- 11) **Clonidine**: Inhibits central generation of NE. Action mediated in the CNS. It has been proposed, where it functions as an α_2 agonist. It acts as a β_2 antagonist results. Clonidine can activate β_2 adrenergic receptors upon higher doses. It causes vasoconstriction by activating α_1 receptors, whereas it causes vasodilation by activating α_2 receptors.

direct +ve chronotropic effects of NE.
However +ve inotropic effects are maintained.

PHENYLEPHRINE: pure α_1 agonist. Not catechol derivative so not a substrate for COMT so has longer duration of action. Effective mydriatic & decongestant & can be used to inc. BP.

Methoxamine: direct acting α_1 agonist. May cause a prolonged inc. in BP due to v.constriction. Also causes vagally mediated bradycardia. Available as inj. Rarely used in hypotensive pts.

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Outline pane showing slide navigation and content:

- Slide 1: This info is locked by a parent...
- Slide 2: **EYE:**
 - Radial muscles of iris α_1 . Its activation causes mydriasis.
 - β agonists have little effect but β antagonists \downarrow production of Aqueous Humor.
 - α agonists increase outflow of aqueous humor from eye & used clinically to dec. IOP.
- Slide 3: **Respiratory System:** (mainly on β_2)
 - Activation of β_2 in bronchial SM leads to Powerful bronchodilation.
 - Bronchial secretion & congestion also decreased.
- Slide 4: **Coastal Glands:**
- Slide 5: **ChE:**
- Slide 6: **Gastrointestinal Tract:**

EYE:

Radial Muscles of iris has α_1 . Its activation causes mydriasis.

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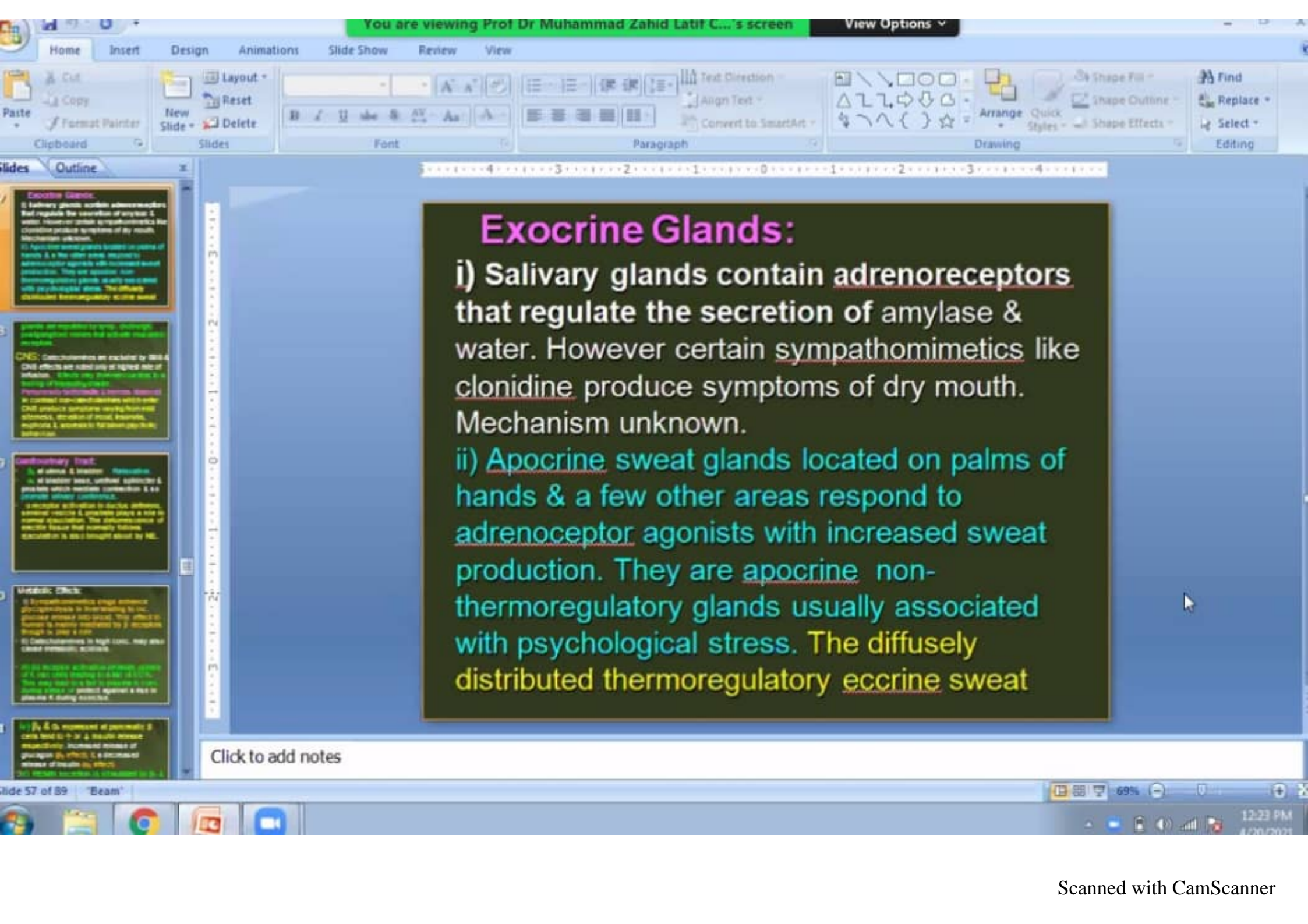
α agonists increase outflow of aqueous humor from eye & used clinically to dec. IOP.

Respiratory System: (mainly on β_2)

Activation of β_2 in bronchial SM leads to Powerful bronchodilation.

Bronchial secretion & congestion also decreased.

Click to add notes



Outline

- Executive Glands:
 - Salivary glands contain adrenoreceptors that regulate the secretion of amylase & water. However certain sympathomimetics like clonidine produce symptoms of dry mouth. Mechanism unknown.
 - Apocrine sweat glands located on palms of hands & a few other areas respond to adrenoceptor agonists with increased sweat production. They are apocrine non-thermoregulatory glands usually associated with psychological stress. The diffusely distributed thermoregulatory eccrine sweat glands are regulated by sympathetic outflow.
- CNS:
 - Clonidine is included by WHO as a CNS effect is noted only at highest rate of infusion. It acts via α_2 receptors to a binding of postsynaptic α_2 receptors.
 - Peripherally acting α_2 agonists, which in contrast to α_2 agonists which enter CNS produce symptoms such as nasal congestion, dryness of mouth, headache, tachycardia & increase in salivary gland secretion.
- Cardiovascular Effect:
 - α_1 of adrenergic & β_1 of adrenergic receptors.
 - α_1 of adrenergic receptors, which are present on vascular smooth muscle & in adrenal medulla.
 - Adrenergic activation to cardiac adrenergic receptors results in increased heart rate & contractility. The performance of cardiac muscle that normally follows excitation is also brought about by β_1 .
- Metabolic Effect:
 - β_1 of adrenergic receptors, which are present on cardiac adrenergic receptors results in increased heart rate & contractility. The performance of cardiac muscle that normally follows excitation is also brought about by β_1 .
 - β_2 of adrenergic receptors, which are present on vascular smooth muscle & in adrenal medulla.
 - Adrenergic activation to cardiac adrenergic receptors results in increased heart rate & contractility. The performance of cardiac muscle that normally follows excitation is also brought about by β_1 .

Exocrine Glands:

i) Salivary glands contain adrenoreceptors that regulate the secretion of amylase & water. However certain sympathomimetics like clonidine produce symptoms of dry mouth. Mechanism unknown.

ii) Apocrine sweat glands located on palms of hands & a few other areas respond to adrenoceptor agonists with increased sweat production. They are apocrine non-thermoregulatory glands usually associated with psychological stress. The diffusely distributed thermoregulatory eccrine sweat

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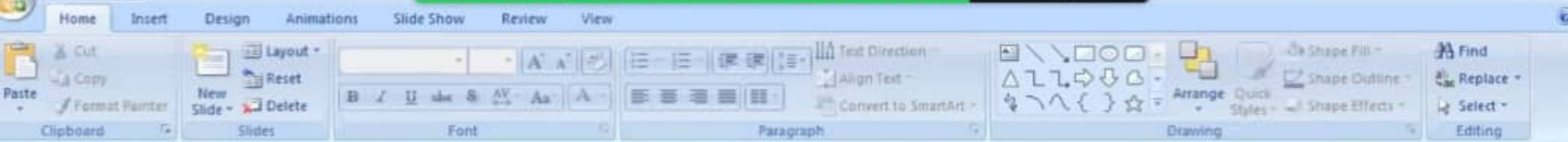
Outline pane showing slide thumbnails:

- Executive Summary
- glands are regulated by symp. cholinergic postganglionic nerves that activate muscarinic receptors.
- CNS: Catecholamines are excluded by BBB & CNS effects are noted only at highest rate of infusion. Effects vary from nervousness to a feeling of impending diaster. Peripherally tachycardia & tremors observed. In contrast non-catecholamines which enter CNS produce symptoms varying from mild alterness, elevation of mood, insomnia, euphoria & anorexia to full blown psychotic behaviour.
- Cardiovascular Tract
- Metabolic Effects

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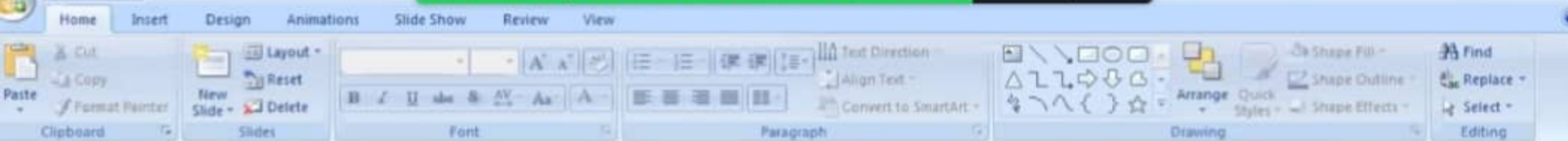
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Genitourinary Tract:

- β_2 at uterus & bladder: Relaxation.
- α_1 at bladder base, urethral sphincter & prostate which mediate contraction & so promote urinary continence.
- α receptor activation in ductus deferens, seminal vesicle & prostate plays a role in normal ejaulation. The detumescence of erectile tissue that normally follows ejaculation is also brought about by NE.

Click to add notes



Outline

Executive Summary

• Primary glands secrete catecholamines that regulate the secretion of insulin and other hormones from the pancreas and the cardiovascular system of the body.

• Adrenaline and noradrenaline are secreted from the adrenal medulla and the sympathetic nervous system. They are secreted in response to stress and are involved in the fight or flight response.

Cardiovascular Effects

• At stress, the sympathetic nervous system stimulates the heart to increase its rate and force of contraction, leading to increased cardiac output.

• The sympathetic nervous system also stimulates the release of adrenaline and noradrenaline from the adrenal medulla, which further increases the heart rate and force of contraction.

Metabolic Effects

• Sympathetic stimulation causes the release of glucose from the liver and the breakdown of glycogen in muscle, leading to increased glucose availability.

• Catecholamines in high concentrations may also cause metabolic acidosis.

• β_2 receptor activation promotes the uptake of K^+ into cells, leading to a fall in extracellular K^+ . This may lead to a fall in plasma K^+ concentration, which may be protective against a rise in plasma K^+ during exercise.

Metabolic Effects:

- i) Sympathomimetics drugs enhance glycogenolysis in liver leading to inc. glucose release into blood. This effect in human is mainly mediated by β receptors though α_1 play a role.
- ii) Catecholamines in high conc. may also cause metabolic acidosis.
- iii) β_2 receptor activation promote uptake of K into cells leading to a fall of EC K . This may lead to a fall in plasma K conc. during stress or protect against a rise in plasma K during exercise.

Click to add notes



Outline

- Genitourinary Tract:**
 - β_1 at uterus & bladder: Prolactin
 - β_1 at bladder base, urethra, sphincter & prostate which mediate contraction & so promote urinary continence.
 - α_1 receptor activation in ducts, detrusor, seminal vesicles & prostate plays a role in normal ejaculation. The absence of either feature that normally follows ejaculation is also brought about by NE.
- Metabolic Effects:**
 - β_1 Sympathomimetic drugs enhance phosphorylation in liver leading to the glucose release into blood. This effect is mainly mediated by β_1 receptors through cAMP & cPK.
 - β_2 Decongestion in high conc. may also cause metabolic alkalosis.
 - β_2 β_2 receptor activation increases synthesis of a new cAMP leading to the release of fatty acids from adipose tissue. This may lead to a fall in plasma K⁺ causing cardiac arrhythmias or protect against a rise in plasma K⁺ during exercise.
 - β_1 & β_2 expression of pancreatic β cells tend to β_1 or β_2 receptors release respectively. Increased release of glucagon (β_1 effect) & a decreased release of insulin (β_2 effect).
 - β_2 NE release is stimulated by β_1 & inhibited by β_2 . Adrenoceptors also modulate the secretion of parathyroid, calcitonin, thyroxine & gastrin. But their significance is limited.
 - β_1 Activation of β_1 in fat cells leads to inc. lipolysis with enhanced release of FFA & glycerol in blood. Epinephrine induces lipolysis through agonist activity on the β receptors of adipose tissue. \uparrow levels of cAMP stimulate a **holoenzyme sensitive lipase**, which hydrolyses triglycerides to free fatty acids and glycerol.
 - β_1 β_1 Human fat cells also contain a fat mobilizing lipase by a β_2 cAMP.
 - β_2 In high conc. epinephrine & related agents cause **myocytolysis**.
- SPECIFIC DRUGS:** Epinephrine, an agonist of both α & β receptors. A very potent vasoconstrictor & cardiac stimulant. It causes \uparrow or \downarrow of BP by its α & β effects & β effects & α effects are involved in many β effects. β_1 also activates β_2 , involves in same β effects. β_2 results in \downarrow of BP by its β_2 effects.

of NE in the periphery at the same time.
 However it may inc. BP in some pts. It frequently causes orthostatic tachycardia.

REBOXETINE similar as atomoxetine.

SIBUTRAMINE: serotonin & NE reuptake inhibitor & only appetite suppressant approved by FDA for long term treatment of obesity.

DULOXETINE: AD with serotonin & NE reuptake inhibitory effects.

COCAINE: LA with peripheral sympathomimetic action that results from inhibition of NE reuptake. Rapidly crosses BBB & produces Amphetamine like effect that is shorter lasting

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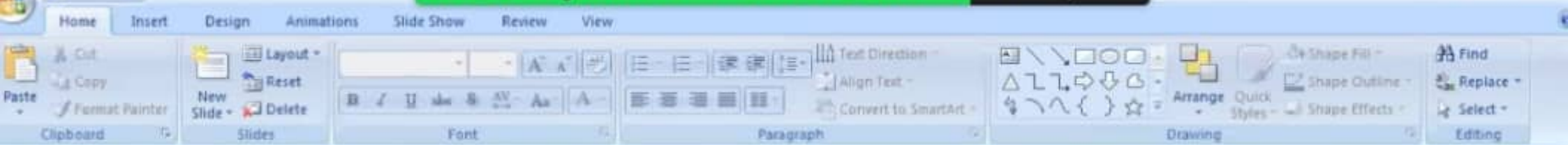


Outline

- ISOPROTERENOL: very potent β agonist. Has +ve chrono & inotropic actions. It is a potent v.dilator becoz it almost exclusively activates β receptors. This leads to a marked inc. in CO associated with a fall in diastolic BP & mean arterial pressure & slight inc. in systolic BP.
- β SELECTIVE AGONIST: seperation of β agonists is imp. becoz they reduce ad. effects.
- β_1 SELECTIVE are DOBUTAMINE & a partial agonist PRENALTEROL. They inc. CO with less reflex tachycardia compared with non-selective β agonists. DOBUTAMINE, chemical structure resembles dopamine but its actions are mediated by activation of α_1 & β_1 receptors. Clinical properties are similar to isoproterenol. Inotropic effect is +ve & chronotropic effect is +ve. It is a potent v.dilator. It is associated with a fall in diastolic BP & mean arterial pressure & slight inc. in systolic BP. Activation of α_1 receptors explains why PRN does not inc. significantly.
- MIXED ACTING SYMPATHOMIMETICS EPHEDRINE: Pentamethylphenol. Being used in China for over 2000 yrs. Introduced in western world in 1848 as a mild acting sympathomimetic. It is a CNS stimulant. It has high reactivity & long duration of action. A large fraction is metabolized in liver. Since it is a weak base, its cardiac action is accelerated by a reduction of pH. It is a weak base & is a red CNS stimulant.
- PSEUDOEPHEDRINE: 1st 4 epinephrine derivatives used as a component of many decongestant solutions. Use of pseudoephedrine as a precursor in manufacture of methamphetamine has led to restriction of sale.
- PHENYLPROPANOLAMINE: a component of over the counter appetite suppressants. Withdrawn from market by neurologic studies in young women. Drug causes BP in pts with impaired adrenergic system.
- INDIRECT ACTING SYMPATHOMIMETICS NARFETHOLINE: imp. for its use as an adrenergic agonist as a CNS stimulant. It is a red CNS stimulant.
- epinephrine: rapidly enters CNS & has marked stimulant effects on heart & vessels. It is a potent v.dilator. Its actions are mediated through release of NE & to some extent dopamine because it enters sympathetic endings & releases stored catecholamines. It is a red CNS stimulant.

- **ISOPROTERENOL**: very potent β agonist. Has +ve chrono & inotropic actions. It is a potent v.dilator becoz it almost exclusively activates β receptors. This leads to a marked inc. in CO associated with a fall in diastolic BP & mean arterial pressure & slight inc. in systolic BP.
- **β SELECTIVE AGONIST**: seperation of β agonists is imp. becoz they reduce ad. effects.
- **β_1 SELECTIVE** are **DOBUTAMINE** & a partial agonist **PRENALTEROL**. They inc. CO with less reflex tachycardia compared with non-selective β agonists. **DOBUTAMINE**, chemical structure resembles dopamine but its actions

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MIXED ACTING SYMPATHOMIMETICS

EPHEDRINE: Plant source(EPHDRA). Being used in China for over 2000 yrs. Introduced in western medicine in 1924 as 1st orally active sympathomimetic drug. Found in Ma huang (herbal medicine) which contains apart from ephedrine multiple ephedrine like alkaloids. Has high bioavailability & long duration of action. A large fraction excreted unchanged in urine. Since it is a weak base, its excretion can be accelerated by acidification of urine. It crosses BBB & is a mild CNS stimulant.

PSEUDOEPHEDRINE: 1 of 4 ephedrine enantiomer

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Slides Outline

- 1. **BIOPHARMACEUTICALS** - very potent & specific, use very common & therefore selective. It is a problem if a patient takes a drug that is not selective for a receptor. This leads to a reduced efficacy of the drug. This leads to a reduced efficacy of the drug. This leads to a reduced efficacy of the drug.
- 2. **SELECTIVE AGONIST**: activation of β_1 receptors & β_2 receptors. β_1 receptors are found in the heart & β_2 receptors are found in the lungs. They are CO-agonists. They are CO-agonists. They are CO-agonists.
- 3. **SELECTIVE ANTAGONISTS** & partial agonists. **PROPRANOLOL**. They are CO-agonists. They are CO-agonists. They are CO-agonists.
- 4. **MIXED ACTING SYMPATHOMIMETICS**. **EPHEDRINE**. Partial agonist. **PHENYLEPHRINE**. Strong agonist. **PHENYLEPHRINE**. Strong agonist. **PHENYLEPHRINE**. Strong agonist.
- 5. **INDIRECT ACTING SYMPATHOMIMETICS**. **AMPHETAMINE**. Imp. b/o its use or misuse as a CNS stimulant. **AMPHETAMINE**. Imp. b/o its use or misuse as a CNS stimulant. **AMPHETAMINE**. Imp. b/o its use or misuse as a CNS stimulant.

(pair of molecule that r mirror image of each other)

used as a component of many decongestant mixtures. Use of pseudoephedrine as a precursor in manufacture of methamphetamine has led to restriction on its sale.

PHENYLPROPANOLAMINE, a component in over the counter appetite suppressants. Withdrawn from market b/o hemorrhagic strokes in young women. Drug can inc. BP in pts with impaired autonomic reflexes.

INDIRECT ACTING SYMPATHOMIMETICS

a) **AMPHETAMINE**: Imp. b/o its use or misuse as a CNS stimulant. P.kinetically similar to

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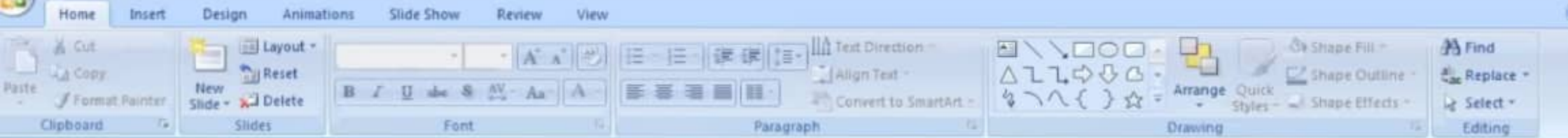
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Slides Outline

ephedrine. Rapidly enters CNS & has marked stimulant effects on mood & alertness & a depressed effect on appetite. Its actions are mediated through release of NE & to some extent dopamine because it enters symp. nerve endings & displaces stored catecholamines. **METHAMPHETAMINE** very similar to amphetamine with an even more higher ratio of central to peripheral actions. **PHENMETRAZINE** has amphetamine like effects & promoted as an anorexiatic & a popular drug of abuse. **Methylphenidate**: Similar to amphetamine. May

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9:58 AM 4/28/202



Outline

sympathetic. readily enters CNS & has marked stimulant effects on mood & attention & a pronounced effect on appetite. Its actions are mediated through release of NE & to some extent dopamine because it enters a wide nerve endings & replaces stored catecholamines. **METHAMPHETAMINE** has similar to amphetamine with an additional higher rate of uptake in dopamine active. **PHENYLETHYLAMINE** has amphetamine like effects & provided as an enantiomer & a popular drug of abuse. **Mephentermine**: Similar to amphetamine. **Modafinil**

be effective in some children with attention deficit hyperactivity disorder.

MODAFINIL: psychostimulant. MOA not fully known; it inhibits both NE & dopamine transporters & inc. interstitial conc. of not only NE & dopamine but also of serotonin & glutamate while dec. GABA levels. **Used in narcolepsy. Causes mild inc. in BP & heart rate.**

TYRAMINE: Normal byproduct of **TYROSINE** metabolism in body. Also found in high conc. in some fermented foods like cheese. **Readily metabolized in liver by MAO. Orally inactive b/o very high 1st pass effect.**

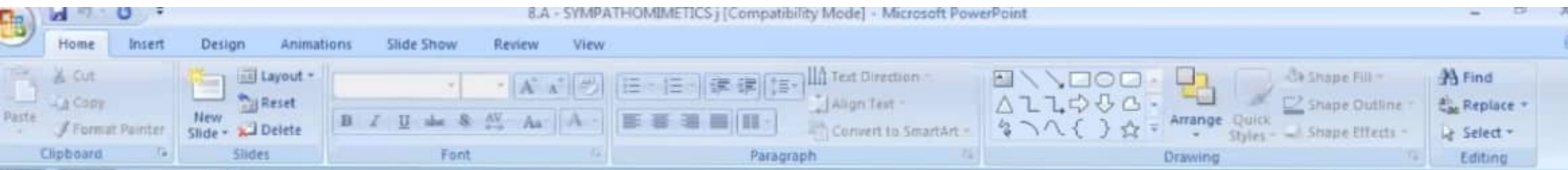
has indirect sympathomimetic effect caused by release of stored catecholamines. **20 times** more potent than amphetamine. **Amphetamine** is a potent stimulant & is readily metabolized leading to a metabolite in the liver. Its effects on MAO inhibitor very potent to avoid tyramine containing foods. **CATECHOLAMINE REUPTAKE INHIBITORS**: They inhibit MAO can inhibit NE & dopamine reuptake. **ATOMOXETINE**: selective inhibitor of NET. Used in attention deficit disorder. It has MAO inhibitor effect but has no effect on CNS & no psychomotor activation with potential for abuse. **if NE in the proximity of the same time. However it also inc. BP in some pts. & frequently causes increased heart rate.** **REBOXETINE**: similar to atomoxetine. **REBURAMINE**: selective MAO inhibitor & only specific reuptake inhibitor by FDA for MAO inhibitor of drugs. **DAJONE**: AD with serotonin & NE reuptake inhibitory effects. **COCAINE**: L.A. with psychomotor stimulant actions that results from inhibition of NE reuptake. **Readily crosses BBB & produces Amphetamine like effects that is greater lasting** but more intense than amphetamine. **Major action of cocaine in CNS is to inhibit dopamine reuptake into neurons by blocking carriers of base. Its toxic effects & the fact that it can be smoked, injected intravenously or inhaled by snorting it or inhaled through a pipe.**

be effective in some children with attention deficit hyperactivity disorder.

MODANIFIL: psychostimulant. MOA not fully known; it inhibits both NE & dopamine transporters & inc. interstitial conc. of not only NE & dopamine but also of serotonin & glutamate while dec. GABA levels. **Used in narcolepsy. Causes mild inc. in BP & heart rate.**

TYRAMINE: Normal byproduct of **TYROSINE** metabolism in body. Also found in high conc. in some fermented foods like cheese. **Readily metabolized in liver by MAO. Orally inactive b/o very high 1st pass effect. Given parenterally**

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Outline

- sympathetic. Usually enters CNS & has marked stimulant effect on mood & attention & a depressant effect on appetite. It acts on mediated through release of NE & to some extent dopamine because it often symp nerve endings & release stored catecholamines. **MAOINHIBITORS** are effective in some children with attention deficit hyperactivity disorder.
- PROCARAZINE** has amphetamine like effects & promotes an increase & a longer time of action.
- MODAFINIL**: psychostimulant, MAO inhibitor. It blocks both NE & dopamine transporters & inc. attention conc. if not only NE & dopamine but also of serotonin & glutamate while dec. GABA levels. **SELECTIVE REUPTAKE INHIBITORS** are used in BP & treat ADHD.
- TYRAMINE**: Normal byproduct of TYROSINE metabolism in body. Also found in high conc. in some fermented foods like cheese. Usually metabolized in liver by MAO. Only builds up very high in liver failure. **DRUG INTERACTIONS**
- has indirect sympathomimetic effect caused by release of stored catecholamines. In pts treated with MAOI esp. A type, effect of tyramine is greatly intensified leading to a marked inc in BP. So pts on MAOI must be very careful to avoid tyramine containing foods.
- CATECHOLAMINE REUPTAKE INHIBITORS**: Tricyclic ADs can inhibit NE & serotonin reuptake.
- ATOMOXETINE**: selective inhibitor of NET. Used in attention deficit disorder. It has little CV effect becoz it has clonidine like effect in CNS to dec. sympathetic outflow while potentiating the effect of NE in the presynaptic & the same time. However it may inc. BP & cause wk. It frequently causes orthostatic hypotension.
- REBOXETINE**: similar to atomoxetine.
- SRITRAMINE**: a selective & NE reuptake inhibitor & only recently approved by FDA for long term treatment of ADHD.
- DALCINETINE**: AD with serotonergic & NE reuptake inhibitory effects.
- COCAINE**: LA with psychomotor stimulants active that results from inhibition of NE reuptake. Usually causes little & produces Amphetamine like effect but is shorter acting.
- but more intense than amphetamine. Major action of cocaine in CNS is to block dopamine reuptake into neurons in presynaptic terminal of DA. This leads to inc. in the DA conc. in synaptic cleft & inc. in the effect of DA on postsynaptic receptors. It also blocks the reuptake of NE & serotonin. Cocaine & amphetamine

has indirect sympathomimetic effect caused by release of stored catecholamines. In pts treated with MAOI esp. A type, effect of tyramine is greatly intensified leading to a marked inc in BP. So pts on MAOI must be very careful to avoid tyramine containing foods.

CATECHOLAMINE REUPTAKE INHIBITORS: Tricyclic ADs can inhibit NE & serotonin reuptake.

ATOMOXETINE: selective inhibitor of NET. Used in attention deficit disorder. It has little CV effect becoz it has clonidine like effect in CNS to dec. sympathetic outflow while potentiating the effect

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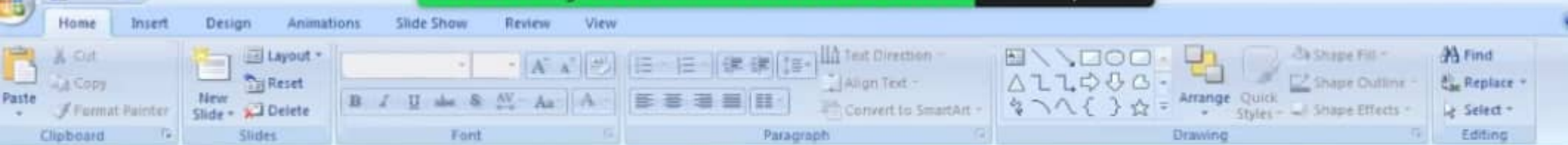
small doses of the catecholamines produce greatly magnified effects in an individual taking *cocaine*. *In addition, the duration of action of epinephrine & NE is increased.* Like *amphetamines*, it can increase BP by α_1 agonist actions and β stimulatory effects.

DOPAMINE AGONIST: LEVODOPA converted to dopamine in body. Used in parkinsonism.

FENOLDOPAM D_1 agonist that selectively leads to peripheral v.dilation in some vascular beds. Used primarily in the IV treatment of severe hypertension.

Outline pane showing slide numbers 1 through 4.

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Uses of sympathomimetic drugs

1. **Acute anaphylaxis:** Syndrome of bronchospasm, mucous membrane congestion, angioedema & severe hypotension respond rapidly to I/M (preferred route) EPI becoz absorption from s/c inj. is unpredictable.
2. As bronchodilator in severe acute bronchial asthma.
3. Inducing local v.constriction & to prolong the action of local anesthetics: EPI is used topically in EPISTAXIS as nasal packs.

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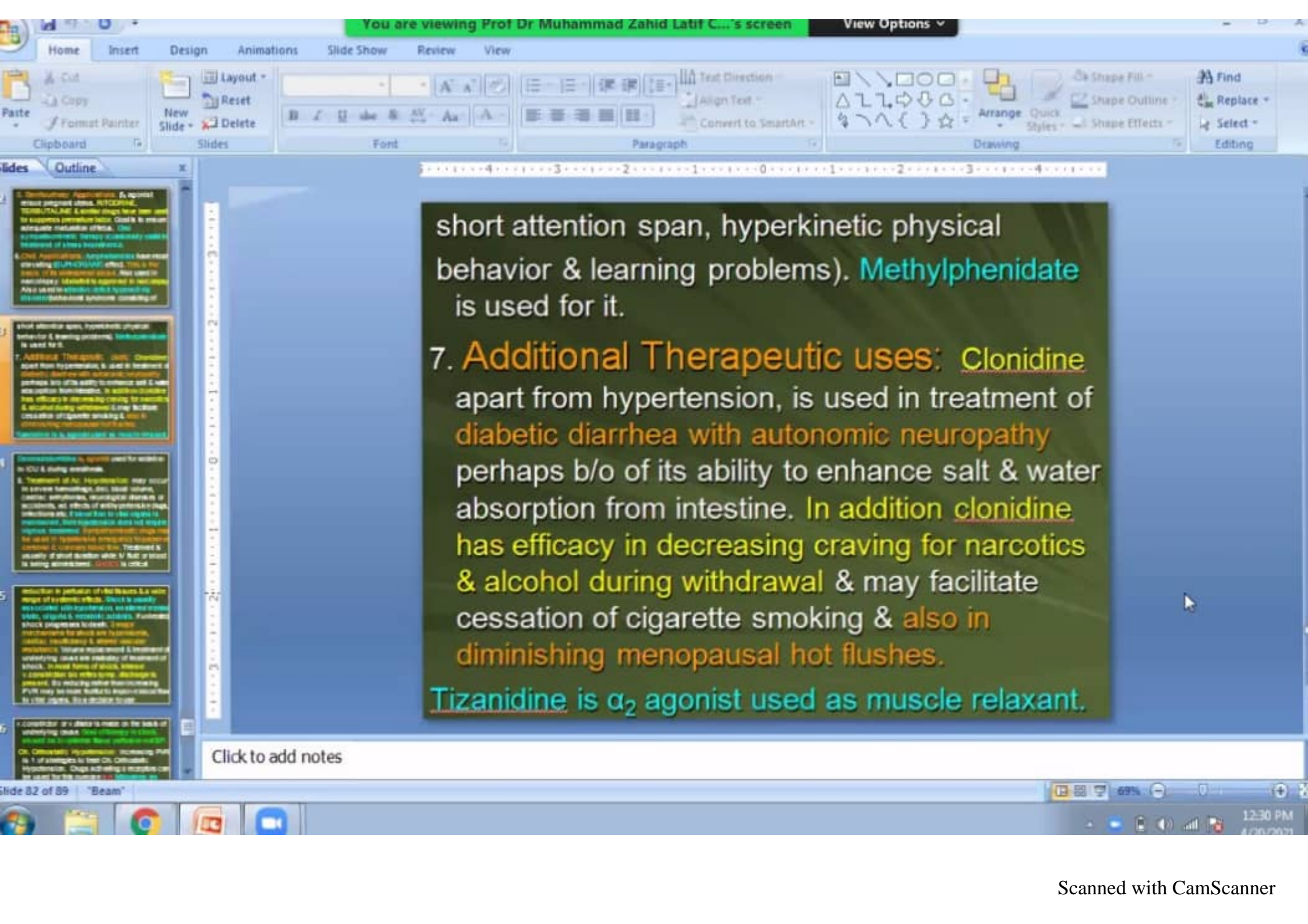
Outline

1. Containing a group with some LOGS, NAE 214767C greatly perhaps conduct of...
agent, it is used as a...
2. Optimal applications...
3. Genitourinary Applications...
4. CNS Applications...
5. Short attention span, hyperactive physical behavior & learning problems...
6. Treatment of Ac. Hypertension...
7. Adrenergic Therapeutic uses...
8. Adrenergic Therapeutic uses...
9. Adrenergic Therapeutic uses...

5. **Genitourinary Applications:** β_2 agonist relaxe pregnant uterus. **RITODRINE, TERBUTALINE & similar drugs** have been used to suppress premature labor. Goal is to ensure adequate maturation of fetus. **Oral sympathomimetic therapy** occasionally useful in treatment of stress incontinence.

6. **CNS Applications:** **Amphetamines** have mood elevating (**EUPHORICANT**) effect. **This is the basis of its widespread abuse.** Also used in narcolepsy. **Modafinil** is approved in narcolepsy Also used in **attention deficit hyperactivity disorder** (behavioral syndrome consisting of

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short attention span, hyperkinetic physical behavior & learning problems). **Methylphenidate** is used for it.

7. **Additional Therapeutic uses:** **Clonidine** apart from hypertension, is used in treatment of **diabetic diarrhea with autonomic neuropathy** perhaps b/o of its ability to enhance salt & water absorption from intestine. **In addition clonidine has efficacy in decreasing craving for narcotics & alcohol during withdrawal & may facilitate cessation of cigarette smoking & also in diminishing menopausal hot flashes.**

Tizanidine is α_2 agonist used as muscle relaxant.

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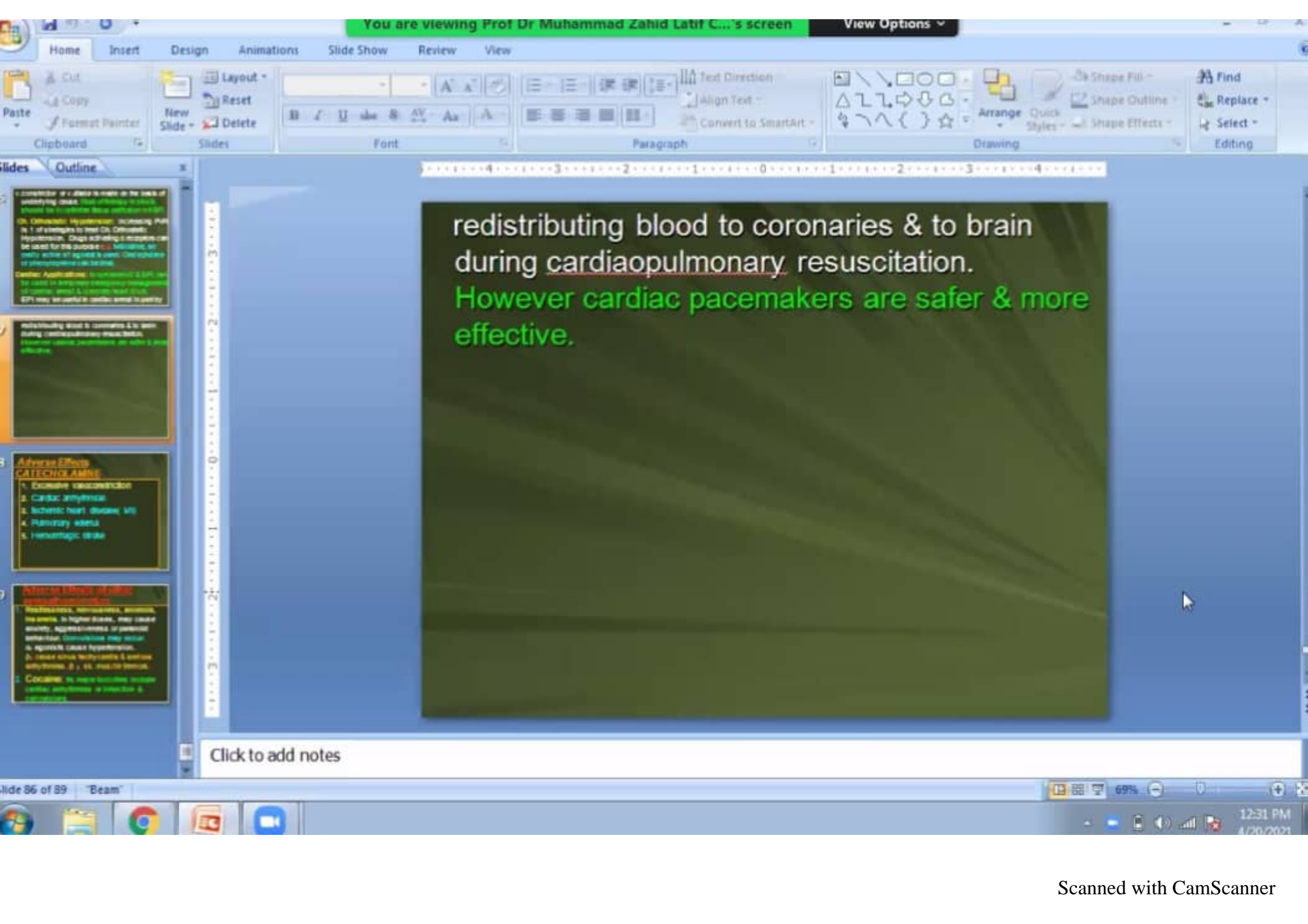


Slides Outline

5. Cardiovascular Applications: An agonist...
 6. CNS Applications: Sympathomimetics have...
 7. Adrenergic Therapies: Isoproterenol...
 8. Treatment of Ac. Hypertension: may occur...
 9. Induction of peripheral (PVR) vasoconstriction...
 10. Consideration: any decision made on the basis of...

reduction in perfusion of vital tissues & a wide range of systemic effects. Shock is usually associated with hypotension, an altered mental state, oliguria & metabolic acidosis. If untreated, shock progresses to death. **3 major mechanisms for shock are hypovolemia, cardiac insufficiency & altered vascular resistance.** Volume replacement & treatment of underlying cause are mainstay of treatment of shock. In most forms of shock, intense v.constriction b/o reflex symp. discharge is present. So reducing rather than increasing PVR may be more fruitful to improve blood flow to vital organs. So a decision to use

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- Shape Effects

Editing

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- Select

Outline

Consideration of a child is made on the basis of underlying cause. Use of drugs to block blood flow to coronaries & to brain during cardiopulmonary resuscitation.

Dr. Diltiazem: Hypertension: Increasing PVR is 1 of attempts to treat Dr. Diltiazem Hypertension. Drugs achieving a response can be used for this purpose. **Adverse:** acutely reduce of aortic & vent. Outflow or myocardial infarction.

Caution: Applications: to prevent a EPI can be used in emergency resuscitation management of cardiac arrest & cardiac heart block. EPI may be useful in cardiac arrest & quality.

Redistributing blood to coronaries & to brain during cardiopulmonary resuscitation. However cardiac pacemakers are safer & more effective.

Adverse Effects
CATECHOLAMINE

1. Excessive vasoconstriction
2. Cardiac arrhythmia
3. Ischemic heart disease inf.
4. Pulmonary edema
5. Hemorrhagic stroke

Adverse Effects of other sympathomimetics

1. **Respiratory:** bronchospasm, asthma, hyperemia, in higher doses, they cause anxiety, apprehensiveness or general excitement. Convulsions may occur.
2. **agitation** cause hypertension.
3. **cause** sinus tachycardia & ventricular arrhythmias. **β₂** & **β₃** may be involved.
4. **Cocaine:** in high doses, cocaine causes arrhythmias or infarction & convulsions.

redistributing blood to coronaries & to brain during cardiopulmonary resuscitation. However cardiac pacemakers are safer & more effective.

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slides Outline

1. Consideration of a patient is made on the basis of underlying illness. This is necessary to check whether the patient is suffering from any other condition which may be affected by the drug.

Dr. Ghassabeh Hypertension: increasing PHH is 1 of the signs to treat. On Onononon Hypertension. Drugs affecting a dopamine can be used for the purpose. In addition, it may be used to control a patient's blood pressure or hypertension can be treated.

Cardiac Applications: In hypertensive & PHH, it is used to improve myocardial metabolism of cardiac vessel & control heart block. EPI may be useful in cardiac arrest in part by

including blood it contains & to aim during cardiovascular resuscitation. However, cardiac stimulants are not a good effective.

Adverse Effects
CATECHOLAMINE

1. Excessive vasoconstriction
2. Cardiac arrhythmia
3. Ischemic heart disease, etc.
4. Pulmonary edema
5. Hemorrhagic stroke

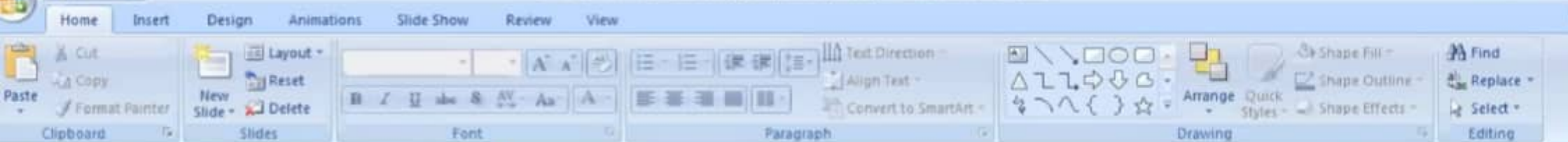
Adverse Effects of other sympathomimetics

1. Restlessness, nervousness, anxiety, insomnia. In higher doses, may cause anxiety, aggressiveness or paranoid behavior. Convulsions may occur.
2. Cocaine: its major toxicities include cardiac arrhythmias or infarction & convulsions.

Adverse Effects of other sympathomimetics

1. Restlessness, nervousness, anorexia, insomnia. In higher doses, may cause anxiety, aggressiveness or paranoid behaviour. Convulsions may occur. α_1 agonists cause hypertension. β_1 cause sinus tachycardia & serious arrhythmias. β_2 sk. muscle tremors.
2. Cocaine: Its major toxicities include cardiac arrhythmias or infarction & convulsions.

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Slides Outline

1. Consider if a slide is made at the level of underlying class. One of many in class should be highlighted. Some performance of...

2. **Dr. Olanzapine Hypertension:** Increasing PVR is 1 of strategies to treat Dr. Olanzapine Hypertension. Drugs affecting a receptor can be used for this purpose. **β₁** agonists, an early action of agonist is used. Olanzapine or atenolol can be used.

3. **Cardiac Applications:** Such as EPI, can be used to improve emergency management of cardiac arrest & complete heart block. EPI may be useful in cardiac arrest in priority.

4. **Adverse Effects**
CATECHOLAMINE

1. Excessive vasoconstriction
2. Cardiac arrhythmia
3. Ischemic heart disease (MI)
4. Pulmonary edema
5. Hemorrhagic stroke

5. **Adverse Effects of other sympathomimetics**

1. Restlessness, nervousness, anorexia, insomnia. In higher doses, may cause anxiety, aggressiveness or paranoid behaviour. **Convulsions may occur.**
2. Cocaine: Its major toxicities include cardiac arrhythmias or infarction & convulsions.

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Adverse Effects of other sympathomimetics

1. Restlessness, nervousness, anorexia, insomnia. In higher doses, may cause anxiety, aggressiveness or paranoid behaviour. **Convulsions may occur.** α_1 agonists cause hypertension. β_1 cause sinus tachycardia & serious arrhythmias. β_2 sk. muscle tremors.
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