(2) Storage of CAs :→ NA is stored in synaptic vesicles or granules with in the adrenergic nerve terminal. The vesicular membrone actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β-hydroxylase.

(NOTE - SEE THE FIGURE-9.4 IN YOUR TEXTBOOK K.D. TRIPATHI)

(3) Release of CAs :→ The nerve impulse coupled release of cA take place by exocytosis and all the vesicular contents (NA & Adr, ATP, dopamine, β hydroxylase, chromogranin) are poured out. In case of vesicles which in addition contain peptides like enkephalin or neuropeptide Y (NPY), these cotransmitters are simultaneously released.

(4) Uptake of CAs :→ There is a very efficient mechanism by which NA released from the nerve terminal is recaptured. This occurs in 2 steps

Axonal uptake :→ An active amine pump (NET) is present at the neuronal membrone which transports NA by a Na^+ coupled mechanism. It takes up NA at a higher rate than Adr and had been labelled uptake-1

Notes ملاحظات

Vesicular Uptake :→ The membrane of intracellular vesicles has another amine pump the 'vesicular monoamine transporter' (VMAT-2), which transports CA from the cytoplasm to the interior of the storage vesicle. The VMAT-2 transports monoamines by exchanging with H^+ ions. The vesicular NA is constantly leaking out into the axoplasm and is recaptured by this mechanism. This carrier also takes up DA formed in the axoplasm for further synthesis to NA.

(5) Metabolism of CAs :→ Part of NA leaking out from vesicles into cytoplasm as well as that taken up by axonal transport is first attacked by MAO, while that which diffuses in circulation is first acted upon by catechol-O-methyl transferase (COMT) in liver and other tissues. The major metabolites excreted in urine are vanillyl mandelic acid (VMA) and 3-methoxy-4-hydroxy phenyl glycol along with some meta nephrine, normetanephrine and 3,4 dihydroxy mandellic acid. These metabolites are mostly conjugated with glucuronic acid or sulfate before excretion in urine.

Notes ملاحظات

(6) Adrenergic Receptors :→ Adrenergic receptors are membrane bound G-protein coupled ~~re~~ receptors which function primarily by increasing or decreasing the intra-

cellular production of second messengers cAMP or IP3 / DAG. In some cases the activated G-protein itself operates K^+ or Ca^{++} channels or increase prostaglandin production. Adrenergic receptors are classified into two types α and β. On the basis of relative organ specificity of selective agonists and antagonists the β receptors were further subdivided into β_1 & β_2. Later β_3 receptors were described which are more sensitive to NA than to Adr. and have low affinity for the standard β blockers.

α receptors also further subdivided into α_1 & α_2.

Mechanism of Action :→

The mechanism of sympathomimetic drugs can be direct acting (Direct interaction between drug and receptors) such as α-adrenergic agonist, β-adrenergic agonists and dopaminergic agonists.

In-direct acting (interaction not between drug and receptor) such as MAOIs (MAO inhibitors), COMT inhibitors, release stimulants, and reuptake inhibitors that increase the levels of endogenous catecholamines.

Notes ملاحظات

3 الثلاثاء TUESDAY 12 Jumada I 1436H

Pharmacological Action

In periphery adrenaline acts on α & β receptors on different tissues and organs. Some important actions are –

Heat :→ • increase the heart rate by acting on β_1 receptors
• Systole is shortened then diastole
• Cardiac output and oxygen consumption markedly increased. increase in atomicity, excitability which cause cardiac arrhythmia.

Blood vessels :→ • Vasoconstrictor (α_1) as well as Vasodilator (β_2), depends on the action of drugs. Action is most marked on arterioles due to α_1 and larger arteries and veins due to β_2.

Blood Pressure :→ • Noradrenaline causes vasoconstriction (α_1), β_1 receptor is responsible for increased in BP. Result - increase in BP, but it cause bradycardia - but adrenaline caused tachycardia.

Notes ملاحظات

Respiratory system :→ Adrenaline, isoprenaline and noradrenaline acts on β_2 of bronchus, result dilation of bronchial smooth muscles. NA potent bronchodilator

(indirectly) but short duration of action.

Eye :→ • Mydriatic occurs due to radial muscles of iris (α_1)

GIT :→ • Gut relaxation occurs through activation of both α & β receptors.
• Peristalsis and sphincture are reduced but is not such effective, so no any clinical importance.

Bladder :→ • Detrusor is relaxed (β_2) and trigone is constrict (α_1) - resulting hinder micturation.

Uterus :→ • Contraction through α while relaxation through β receptors.

Skeletal muscles :→ • Contraction of muscles
• Tension develops in muscles fibres which may cause tremor mediated by β-receptors.

CNS :→ • Clinical dose of adrenaline produce no any marked ~~mar~~ effects on CNS, because of poor penetration of BBB. When injected in brain it produced excitation followed by depression.

Notes ملاحظات

5 الخميس THURSDAY 14 Jumada I 1436H ١٤ جمادى الأولى ١٤٣٦هـ

Metabolic :→
- Increase blood glucose levels by increasing the cAMP in liver cell and stimulating glycogenolysis through β_2 receptors.
- Gluconeogenolysis and glycogenolysis may cause increase glucose level in blood.

Glands :→
- decrease the secretion of glands.

—: Adverse Effects :—
- Restlessness
- Palpitation
- Tremor
- Anxiety
- Tachycardia
- Marked rise in BP
- Cerebral hemmorage
- Cardiac arrest.

Note:—
See the important adrenergic drugs in textbook. like dopamine, dobutamine, etc.

Notes ملاحظات

الجمعة
FRIDAY
6
١٥ جمادى الأولى ١٤٣٦هـ
15 Jumada I 1436H

SYMPATHOLYTIC
OR
ANTIADRENERGIC DRUGS

These are drugs which antagonize the receptor action of adrenaline and related drugs. They are competitive antagonist at α or β or both α & β adrenergic receptors and differ in important ways from adrenergic neurone blocking agents which act by interfering with the release of adrenergic transmitter on nerve stimulation.

WEEK 10
03

α- Adrenergic blocking drugs :-

السبت
SATURDAY
7
١٦ جمادى الأولى ١٤٣٦هـ
16 Jumada I 1436H

These drugs inhibit adrenergic responses mediated through the α-adrenergic receptors without affecting those mediated through β receptors.

Notes
ملاحظات

8 الأحد SUNDAY 17 Jumada I 1436H ١٧ جمادى الأولى ١٤٣٦هـ

— ° Classification °.—

(1) Nonequilibrium Type
(i) β-Haloalkylamine - Phenoxybenzamine

(2) Equilibrium Type (competitive)
(A) Non-Selective
(i) Ergot alkaloids - Ergotamine
Ergotoxine
(ii) Hydrogenated ergot alkaloids - Dihydroergotoxine
Dihydroergotamine
(iii) Imidazoline - Phentolamine
(iv) Miscellaneous - Chlorpromazine

(B) α_1 Selective - Prazosine, Terazosine
Doxazocine, Alfuzosine
Tamsulosine

(C) α_2 Selective - Yohimbine

Notes ملاحظات

General effects of α Blockers :—

(1) Blockade of vasoconstrictor α_1 (also α_2) receptors reduces peripheral resistance and causes pooling of blood in capacitance vessels → venous return and cardiac output are reduced → fall in BP. Postural reflex is interfered with → marked hypotension occurs on standing → dizziness and syncope.
The α blockers abolishes the pressor action of Adr, which then produces only fall in BP due to β_2 mediated vasodilatation.

(2) Reflex tachycardia occurs due fall in mean arterial pressure and increased release of NA due to blockade of presynaptic α_2 receptors.

(3) Nasal stuffiness and mioses result from blockade of α receptors in nasal blood vessels and in radial muscles of iris respectively.

(4) Intestinal motility is increased due to partial inhibition of relaxant sympathetic influences - loose motion may occur.

(5) Hypotension produced by α blockers can reduce renal blood flow → G.F.R is reduced and more complete reabsorption of Na^+ retention and expansion of blood volume. This is accentuated by reflex increase in renin release mediated through β_1 receptors.

Notes

(6) Tone of smooth muscles in bladder trigone, sphincter and prostate is reduced by blockade of α_1 receptors → urine flow in patients with benign hypertrophy of Prostate (BHP) is improved.

(7) Contraction of Vas deferens and related organs which result in ejaculation are coordinated through α receptors — α blockers can inhibit ejaculation; this may manifest as impotence.

The α blockers have no effect on adrenergic cardiac stimulation, bronchodilatation, vasodilatation and most of the metabolic changes, because these are mediated predominantly through β receptors.

← ∘ Uses of α-Blockers :→

See your textbook for this

K. D. Tripathi

Notes ملاحظات

:- β-Adrenergic Blocking Drugs :-

These drugs inhibit adrenergic responses mediated through the β receptors. All β blockers are competitive agonists. Propranol blocks β_1 and β_2 receptors, but has weak activity on β_3 ~~receptors~~ subtypes.

Classification :-

Nonselective (β_1 and β_2)

(a) Without intrinsic sympathomimetic activity -
Propranolol, Sotalol, Timolol

(b) With intrinsic sympathomimetic activity -
Pindolol

(c) With additional α blocking property -
Labetolol, Carvedilol

Cardioselective (β_1)
Metoprolol, Atenolol, Acebutolol, Bisoprolol, Esmolol, Betaxolol, Celiprolol, Nebivolol.

ملاحظات
Notes

PHARMACOLOGICAL ACTION :-

Mechanism of Action :-

Antiadrenergic agents inhibit the signals of epinephrine and nor-epinephrine. They are primarily postsynaptic adrenergic receptor antagonists, ~~inhibitor~~ inhibiting the downstream cellular signalling pathways of adrenergic receptors. However there are exceptions; clonidine is an adrenergic agonist at the α_2 receptor. Since this receptor is located presynaptically, agonism at this receptor inhibits the presynaptic release of adrenaline and noradrenaline, preventing postsynatic adrenergic receptor activation and downstream signalling.

Another way to inhibit adrenergic receptor singnaling is by is by blocking the synthesis of catecholamines. Methyltyrosine, for example, inhibits one of the key engyme in pathway tyrosine hydroxylase.

Notes ملاحظات

72-293

22 Jumada I 1436H ٢٢ جمادى الأولى ١٤٣٦هـ

الجمعة FRIDAY **13**

Heart :→ • Propranolol decreare heart rate, force of contraction (at relatively higher doses) and Cardiac output.
• Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic pressure decreases.
• The overall effect in angina patients is improvement of O_2 supply / demand status : exercise tolerance is increased.

Blood vessels :→ • Propranolol blocks vasodilatation and fall in BP evoked by isoprop isoprenaline
73-292 and enhances the rise in BP caused by Adrenaline.
• Propranolol has no direct effect on blood vessels and there is little acute change in BP.
• Total peripheral resistance (T.P.R) is increased initially (due to blockade of β_2-mediated vasodilatation) and cardiac output is reduced, so that there is little change in BP.
• Reduced NA release from sympathetic terminals due to blockade of β receptor mediated facilitation of the release process.

23 Jumada I 1436H ٢٣ جمادى الأولى ١٤٣٦هـ

السبت SATURDAY **14**

Respiratory tract :→ Propranolol increases bronchial resistance by blocking bi dilator ملاحظات β_2 receptors. In asthmatics, however the condition is consistently worsened and a severe attack may be precipitated.

Notes

15 الأحد SUNDAY 24 Jumada I 1436H ٢٤ جمادى الأولى ١٤٣٦هـ

CNS :→ No overt central effects are produced by propranolol. However, subtle behavioural changes, forgetfulness, increased dreaming and nightmares have been reported with long-term use of relatively high dose.

Local anaesthetic :→ Propranolol is as potent a local anaesthetic as lidocaine, but is not clinically used for this purpose because it causes irritation at the injected site.

Metabolic :→ Propranolol blocks adrenergically induced lipolysis and consequent increase in plasma free fatty acid levels:
- Plasma triglycerids level and LDL/HDL ratio is increased during propranolol therapy.
- It also inhibits glycogenolysis in heart, skeletal muscles and in liver, which occurs due to Adr release during hypoglycemia - recovery from insulin action is delayed.

Skeletal muscles :→ Propranolol inhibits adrenergically provoked tremor. This is a peripheral action exerted directly on the muscle fibres (through β_2 receptors).

Notes ملاحظات

Eye :→ Instillation of propranolol and some other β blockers reduces secretion of aqueous humor i.o.t. is lowered.

MARCH 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
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JUMADA I - JUMADA II 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 1 2 3 4 5 6 7 8 9 10 11

Uterus :→ Relaxation of uterus in response to isoprenaline and selective β_2 agonists is blocked by propranolol.

Interactions :→

(1) Additive depression of sinus node and A-V conduction with digitalis and verapamil — cardiac arrest can occur.

(2) Propranolol delays recovery from hypoglycemia due to insulin and oral antidiabitic.

(3) Phenylephrine, ephedrine and other α agonists present in cold remedies can cause marked rise in BP due to blockade of sympathetic vasodilatation.

(4) Indomethacin and other NSAIDs attenuate the anti-hypertensive action of β blocker.

(5) Propranolol retards lidocaine metabolism by reducing hepatic blood flow.

(6) Propranolol increases bioavailability of chlorpromazine by decreasing its first pass metabolism.

Notes ملاحظات

Note :-

For ADVERSE EFFECT & CONTRAINDICATIONS please refer your textbook.