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Novel Mode Of Actions (MOAs) Of Marine Cardioactive Biomolecules (MCBs)

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Abstract:

MCBs have antianginal, antiarrhythmic, antihyperlipidemic, antihypertensive and cardiotonic types of bioactivities. MOAs of MCBs followed the basic cardiopharmacological mechanisms. The structural uniqueness of Autonomium chloride, Anthopleurine A, marine toxins and nucleosides imparted new clues of mechanisms. The stereoselective drug action of Octopamine was topographically rationalized.

1.Introduction

Modern or 20th century development of advanced medicinal chemistry which is equivalent to molecular pharmacology for the discovery and designing of novel therapeutic agents have elegantly emerged with great success. Marine biomolecules have secured distinctions at therapeutic front. It encouraged us to gauge the cardioactive potential of marine biomolecules. The cardioactive biomolecules are anionic (acidic) and cationic (basic), therefore they have ionic character.

Recent development in marine pharmacology has explored biomedicinal potential of cardioactive marine biomolecules[3]. Antianginal, antiarrhythmic, antihypertensive, cardiotonic activities are encountered in MCBs.

2.Theoretical Methodology

MOAs are delineated for rationalizing the roles of their structural uniqueness in drug action.

- Antianginal MCBs- They should have vasodilatory effect and are useful in coronary heart disease. Ca^{++} channel antagonists block the L-type Ca^{++} channels specifically present in heart and vascular smooth muscles. They are potent arteriolar vasodilators so effective in antianginal therapy.
- Omega-3 fatty Acids[4,5]-Eicosapentaenic acid (EPA) and Docosahexaenoic acid (DHA) (omega3-fatty acids) are conventionally formulated in fish oil capsule. They have cardioprotective effect in coronary heart disease because they decrease creatine kinase, lactate dehydrogenase and serum triglycerides. Their antiatherogenic effect is therapeutically beneficial as they decrease platelet aggregation. 2,2 dimethyl EPA is very potent. This enhances fatty acyl CoA oxidase action (beta oxidation).
- Antiarrhythmic MCBs- Antiarrhythmics modify and restore normal cardiac rhythm. Arrhythmias are due to disorder of electrical impulse formation by disturbances in impulse conduction through the myocardium. They act by blocking Na^{+}, K^{+}, Ca^{++} ion channels. Voltage gated Na^{+} channel blockers reduce the excitability of nodal regions of heart. They prevent Ca^{+} mediated depolarization in SA-node and Purkinje fibres.
- Omega-3 fatty Acids (EPA and DHA)[4]

- They are potent inhibitors of voltage gated Na^+ channels and have stabilizing effect on myocardium; therefore, they are useful in ventricular dysrrhythmias. EPA and DHA prevents calcium preload by maintaining the activity of L-type calcium channels during periods of stress and enhance activity of cardiac microsomal Ca^+/Mg^{++} ATPase.

- Saxitoxin and Tetrodotoxin[2,6-10]
    - Marine toxins sensitive Na^+ channels are present in the mammalian heart. They are selective blockers of voltage gated Na^+ channels and cause no damage in action potential. Their receptor site is pore site 1, therefore are also known as "poreblockers". Pore is made of large alpha subunits and small beta subunits. TTX and STX bind to site 1 located at extracellular pore opening of the ion channel.
    - TTX is amphoteric with unique tricyclic structure. It has both cationic (guanidine) and anionic (acid-hydroxyl) groups. The positively charged guanidium group interacts with negatively charged carboxylic group at pore of Na^+ channel on extracelluar side of plasma membrane.
    - STX is also tricyclic but has two guanidinium moieties.

- Antihyperlipidemic MBCs : They are hypolipidemic, and lipid regulators.
- Eckol[11]- It decreases triglycerides, total cholesterol, and LDL-C which are attributed to antihyperlidemic effect.
- Antihypertensive MCB's[2,3] : Antihypertensives act by lowering the sympathetic tone or vasopressor activity. They also inhibit biosynthesis of Octapeptide, mediated by angiotensin converting enzyme in nephron. They block release of nitric oxide and ET 1 factor from active endothelium.
- Marine peptides[12]- They are ACE inhibitory peptides. They inhibit angiotensin-1 converting engyme.
- Prostaglandins[13] – Participate in antihypertensive action by inhibition of angiotensin converting enzyme (ACE) and angiotensin type 1 (AT 1) Receptor antagonist.

- Phlorotannins[5,11] - They are phenolic compounds and formed the polymerization of phloroglucinol (=1,3,5-hydroxybenzene). They form a complex with protein and glycoproteins to inhibit ACE activity. It involves sesquestration of the enzyme metal factor Zn^{2+} ion.
- Marine nucleosides[2]- Adenosinergic[14] and purinergic receptors[15] are targets for caffeine, adenosine and marine nucleosides. Adenosine is cardioprotective nucleoside which signals the activation of A_3 –subtype Rs (seven-transmembrane alpha helices) for
- Preservation of ATP levels
- Stimulation of glycolysis
- Limitation of oxygen demand
- The functional role of purines and pyrimidines acting on purinergic Rs (Subtype P2) are implicated in the regulation of heart. ATP; UTP and UDP have cardioprotective roles.
- Marine nucleosides[3] (Spongosine, Doridosine, and Spongouridine) have close structural resemblances with adenosine and guanosine, therefore their interactions with adenosine Rs and purinergic Rs exhibited cardiovascular effects. They are:
- Decreased heart rate and force of cardiac contractibilty.
- Negative inotropic effect.
- Vasodilation
- Enhanced coronary blood flow.
    - Their potencies in increasing vasodilation and coronary flow are:
    - Adenosine>Spongosine>Isoguanosine>Dridosine (most potent hypotensive)

- TTX[6]-Reduction in arterial blood pressure results from a reduced total peripheral resistance (TPR) and reduced cardiac output and vasomotor tone.

- Cardiotonic MCB's[2] – Cardiotonics have therapeutical value in congestive heart failure (CHF) or myocardial infarcation. They increase the contractile force of the heart and have positive inotropic properties. They improve cardiac output and oxygen consumption per minute, thus cardiac efficacy is improved.

Haemodynamically kidney and heart have interdependent physiological relationship. The enhanced renal blood flow decrease ventricular preload and edema fluid.

- Halenaquinol[16]- It inhibits membrane transport enzyme Na^+ K^+ ATPase SAR studies found that this inhibition is dependent on naphthohydroquinone fragment of the structure.
- Xestoquinone[17,18]- enhancement of intracellular cyclic AMP and Ca^{2+} influx across myocardial membrane impart cardiotonic response. The strong inotropic activity is due to inhibition of Na^+ K^+ ATPase.
- Autonomium chloride[2,3,19]- Autonomium chloride has dual adrenergic and cholinergic actions.

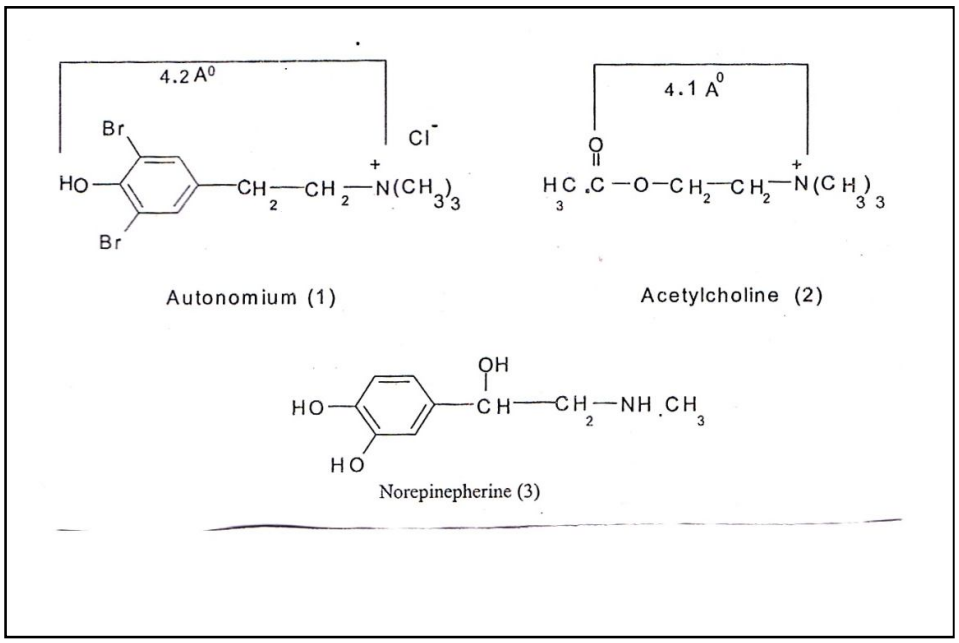

Figure 1

- Anthopleurine- A^3: potent positive inotropic effect, without chronotropic action. It is claimed that translocation of intracellular Ca^{2+} rather than extracellular influx of Ca^{2+} may be involve in MOA of APA. It is 200x more potent than DIgoxin, AP-A does not effect Na^+ K^+ ATPase but has direct action on cardiac muscles and increase myocardial contractibilty
- Octopamine[2,20]- Octopamine is a chiral marine biomolecule. It shares phenylethyl amine side chain of adrenomimitics (Norepinephrine and ephedrine).The structural similaritywith norepinephrine, and ephedrine imparted adrenoreceptor

agonism with mixed MOA's. Octopamine is mixed adrenomimitic, because it causes activation of adrenoreceptors (NE) and release of catechol amines from storage sites or inhibiton of their uptake (ephedrine).

2.Discussion And Result

The basic principles of cardiovascular bioactions are followed by MCBs. The uniqueness of their MOAs are :-

- Autonomic nervous system (ANS) regulates cardiovascular physiology. Autonomium chloride mimics adrenergic and cholinergic neurotransmitters at structural level, for balancing normal cardiac functionality.

This is attributed to interatomic similarity with acetylcholine and phenolic and ethylenic similarity with adrenaline. Possibly it may balance cholinergic and adrenergic systems in CNS for normal cardiovascular physiology.

- Anthopleurine A is 200x times more potent than Digoxin, the classical feature of digitalis-strophanthus type of cardenolides are invalidated by MCB. It has peptide structure which has no affect on Na^+, K^+ ATPase but directly acts on cardiac muscle and enhance myocardial contractibilty.
- Saxitoxin and Tetrodotoxin act as " Pore blockers" at site 1 of voltage gated sodium channels,without any change in action potential.
- Marine nucleosides interact with adenosinergic and purinergic Rs, producing negative inotropy, vasodilation and coronary flow, which are therapeutically useful in cardiac ailments.
- Octopamine is chiral name marine biomolecule has mixed action of adrenomimetics.

  The natural D(-) isomer is 3x more potent than L (+). This stereoselectivity can be explained in the following manner.

2.1.Interaction Of Octopamine Isomers With Adrenoreceptors

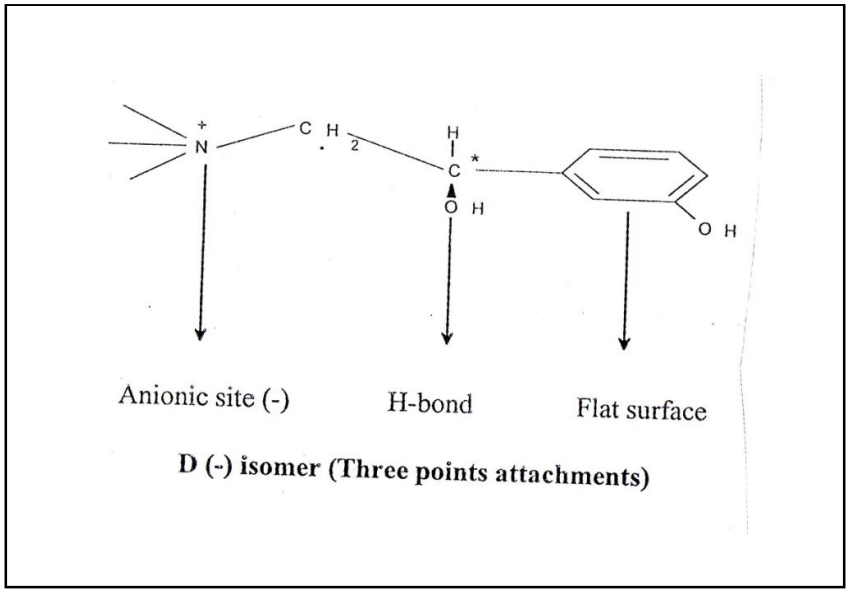

Figure 2

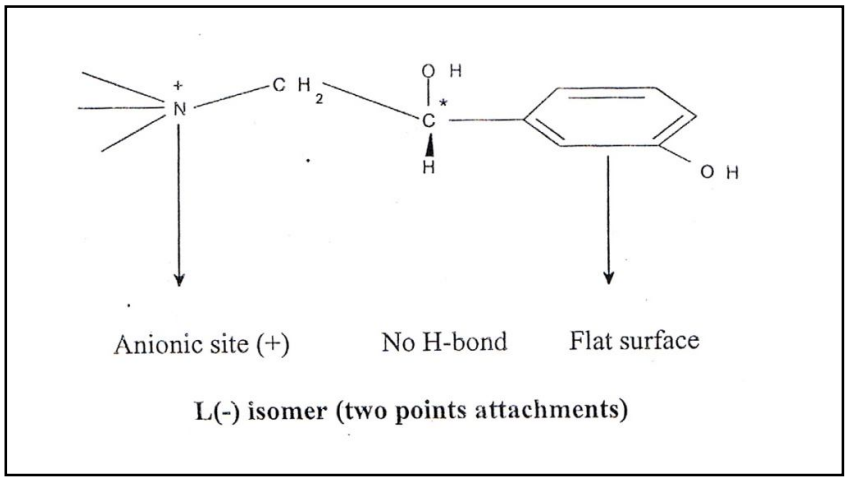

Figure 3

The D(-) isomer has more binding sites than L(+),therefore it is more active.

3.Conclusion

The structural uniqueness of MCBs shared basic MOAs of cardiovascular drugs. Their MOAs exhibited more than one cardiac activity at therapeutic level.Marine novel

chemical entities have great potential for the therapeutical exploration in cardiac vascular medicines.

4.Acknowledgement

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