**MED3ATB**

**Cardiomyopathy worksheet**

**Instructions**

Fill out the following worksheet while working through the *Cardiomyopathy* lesson on LMS. You must write all answers in your own words (paraphrase). Do not plagiarize from the text or videos provided!

Bring your worksheet to the workshop. You will be tested on your knowledge of this module in the weekly quiz.

1. What are second messengers? Explain the roles of two important second messengers in cardiac contractile function (5-6 sentences). **5 Marks**

Second messengers are intracellular substances that conduct cell signaling upon being activated by binding of various extracellular molecules including hormones and neurotransmitters to their cell surface receptors.

Cyclic AMP (cAMP) and Ca2+ are important second messengers that mediate heart muscle contraction.

Once activated, cAMP binds to the regulator subunits of inactive Protein Kinase A (PKA) and cause conformational changes in them.

Consequently, the catalytic subunits of PKA get dissociated from the PKA tetramer and thereby get activated.

Activated catalytic PKA subunits then bind to the cell surface Ca2+ channels and promote Ca2+ influx which essentially drives the regulation of heart muscle contractions.

1. Catecholamine signalling can have different effect in different tissues, explain (4-5 sentences) **5 Marks**

Catecholamines such as adrenaline and noradrenaline can have different effects on different tissues depending on the type of receptors they interact with on the tissue surface and the different downstream signaling pathways that get activated as a result.

When catecholamines bind to different receptor classes, depending on the combination of transducers, second messengers and effector molecules that get activated in the particular downstream signaling pathway, the cellular response may vary.

For example, binding of adrenaline to β1 adrenergic receptors on the myocardium surface leads to a Ca2+ influx and therefore, increased contractility.

However, binding of adrenaline to the cell surface β2 adrenergic receptors on bronchioles lead to the desensitization of those cells to Ca2+ causing them to relax (dilate).

1. Explain how cyclic AMP leads to PKA activation (3 sentences). **3 Marks**

Inactive protein Kinase A (PKA) is a heterotetramer made up of two regulatory subunits and two catalytic subunits. Upon activation, cyclic AMP binds to the regulatory subunits of PKA and cause a conformational change in them that leads to the dissociation of the catalytic subunits. Released catalytic subunits are active and therefore, can enable their kinase activity by phosphorylating downstream proteins.

1. Explain different ways of regulating AR signalling (5 sentences) **5 Marks**
2. Phosphodiesterases hydrolyze cAMP and lead to its inactivation by converting it to a different molecule.
3. Phosphorylated downstream protein targets of Ser/Thr kinase, PKA, get dephosphorylated by Ser/Thr phosphatases and inhibit downstream signaling pathways.
4. Binding of G-protein to activated G-protein coupled receptor (GPCR) can be inhibited by G-protein linked receptor kinases (GRK) that dephosphorylate selected Ser/Thr residues on the receptor. This provides a docking site for arrestin that inactivates/desensitizes the GPCR.
5. Binding of arrestin to such docking sites sometimes facilitates the internalization of GPCR through clathrin-dependent endocytosis and prevents the hormone/neurotransmitter-receptor interaction on the cell surface.
6. If the cAMP concentrations increase due to the occupied GPCRs, activated downstream PKAs act on a negative feedback loop to phosphorylate the GPCR and leads to its inactivation/ desensitization.
7. What is the need for developing new drugs than beta-blockers for treating heart failure? (3 sentences) **3 Marks**

Although beta-blockers are effective therapeutics for cardiomyopathy, they also display many off-target adverse events such as bronchospasm in asthma patients.

As beta blockers administer their function through inhibiting the beta receptors on myocytes that are essential for cardiac contractility, high dosages of the drug may cause for the patient’s heart to stop beating.

Since determining a maximum tolerated dose for beta blockers is also challenging, exploring potential drugs that target the signaling pathway downstream of the beta receptors to prevent the recruitment of the proapoptotic BIM and inhibit the contribution of activated PKA pathway in cardiac contractility maybe a viable option.