LSC204 Main exam 2022
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1. Detail the homeostatic mechanism that determine mean arterial blood pressure.

Mean arterial blood pressure is determined by Ohm's law altered for dynamics of fluid. It explains that total peripheral resistance and cardiac output are proportional to blood pressure. However, blood pressure relies on the combined activity of several systems. The brain has parasympathetic and sympathetic interventions to the vasculature and heart. It affects the vessel diameter and the heart rate and force. The kidneys also play an important role in monitoring blood pressure. The aldosterone production is part of the very powerful vasoconstricting and sodium retaining renin-aldosterone-angiotensin system.

The main determinant of total peripheral resistance is the arteriolar radius, which is influenced by two principal categories. The intrinsic control produces local changes to arteriolar smooth muscle in the vicinity to match the appropriate blood flow through a tissue depending on its metabolic needs. On the other hand, extrinsic control is the main factor affecting the regulation of blood pressure and it is controlled by sympathetic influence on arteriolar smooth muscle.

Extrinsic sympathetic control of arteriolar radius is important in regulating blood pressure. This is reflected in the stimulation of generalized arteriolar vasoconstriction when sympathetic activity has increased. Arteriole vasoconstriction decreases blood flow and increases resistance. Vasoconstriction increases circular smooth muscle contraction in the arteriolar wall, leading to higher resistance and decreased flow through the vessel. On the contrary, decreased sympathetic activity leads to generalized arteriolar vasodilation. Arteriolar vasodilation decreases resistance and increases blood flow through the vessel. Vasodilation causes a lower circular smooth muscle contraction in the arteriolar wall, which leads to decreased resistance and increased flow through the vessel.

Several hormones influence blood pressure. Vasopressin, a peptide hormone that acts on the kidney, and angiotensin II are vasoconstrictors that play an important role in fluid balance. Arteriole vasodilation relies on the production of nitric oxide (NO). Regulated by endothelial cells, NO enters the smooth muscle cell and activates the enzyme guanylate cyclase to produce cGMP and activate PKG, stimulating relaxation. Endothelin is a potent vasoconstrictor. Its release is stimulated by Ang II, reactive oxygen species, cytokines, ADH, and shearing forces acting on the vascular endothelium. It triggers intracellular calcium release and the production of IP3.

The total peripheral resistance is also affected by blood viscosity. It is altered with the level of haematocrit, which is the percentage of red blood cells in the total blood volume. An elevated number of red blood cells increase viscosity.

The cardiac output relies on stroke volume and heart rate, both are affected by adrenaline level and sympathetic activity. Parasympathetic activity decreases heart rate. Ventricular stroke volume is elevated by high end-diastolic volume, which is also increased by raised atrial pressure. A growth in atrial pressure is stimulated by elevated venous return, increasing venous pressure and blood volume.

The renin-angiotensin aldosterone system is a potent hormonal system that regulates blood pressure in the long term. It responds to osmolarity, the measure of the concentration of all the chemicals in the blood, and a decrease in blood volume. In the kidney, a decreased filtrate flow rate stimulates the nephron, the macula densa in particular, to trigger the granular cells and release renin.

Renin affects the peptide produced by the liver, the angiotensinogen. This is transformed to angiotensin 1 which is smitten to angiotensin 2 (AngII) by the protein ACE of some epithelial cells. AngII causes increase blood pressure due to the stimulation of the central nervous system to increase sympathetic output. AngII is also a potent vasoconstrictor that can increase arteriole constriction. In addition, this final protein hormone triggers the adrenal cortex to release aldosterone, increasing sodium absorption. Therefore, vasopressin and aldosterone increase blood volume by elevating salt and water absorption.

In conclusion, the regulation of arterial blood pressure is a complex multi-system process that is determined by peripheral resistance and cardiac output. Therefore, the control of arteriolar radius, blood viscosity, stroke volume, and heart rate influence the homeostatic mechanism that determines arterial blood pressure.

2. Discuss the main events that occur during sperm passage through the female reproductive tract, from being deposited in the vagina up until the point of successful fertilisation.

The fertilisation journey starts with sperm deposition in the vagina. Around 300 million spermatozoa are exposed to antimicrobial defences such as the acidic environment in the vagina and immunological responses. A lower PH protects the area from pathogens; however, the PH is rapidly increased to allow the spermatozoa a few minutes to go through the cervix. Although some of them will die, many will survive due to the protective fluid surrounding the sperm.

The cervix usually remains closed, but it widens when a woman ovulates and when it is influenced by estrogen, releasing highly hydrated mucus, and facilitating the passage of sperm. The cervical mucus has watery consistency since the higher the level of hydration, the easier will be for the sperm to penetrate and continue its journey. Millions will die trying to make it through the mucus due to poor morphology or motility. In addition, they can get caught in the folds of the cervix or get attacked by immune responses. The sperm swim through the cervical mucus and continue swimming towards the uterus.

The survivors enter the uterus. Around 14 million sperm are left at this stage. Muscular uterine contractions in the myometrium assist the transport of sperm. This can lead to a higher rate of spermatozoa survival due to the reduction of the time they spend on the uterus. The woman's immune system destroys thousands of sperm because they recognize the sperm as foreign. As time passes, they become more susceptible to leukocytic attacks. A fast uterine passage is important to avoid the arrival of a significant number of phagocytes.

The few thousand sperm left access to the fallopian tubes. Half of the sperm left continue to the empty fallopian tube and the other half go to where the unfertilized egg is. Spermatozoa search for the motion caused by tiny cilia when pushing the egg toward the uterus to reach the egg. Some sperm get trapped in the cilia and die. Due to the chemotaxis, sperm swim up the concentration gradient towards the egg. At the same time, chemicals released from the female tract stimulate the capacitation process. This consists of changes to the acrosome membrane in order to prepare the sperm for the acrosome reaction. Moreover, spermatozoa become hyperactive, swimming more effectively, faster, and harder through the mucus of the ampulla.

A few dozen of sperm reach the egg. The spermatozoa must push through corona radiata to reach the outer layer of the egg, also called zona pellucida. At this moment, the acrosome reaction is triggered. Consequently, the sperm attach to specialized sperm receptors on the surface, such as the protein ZP3. This triggers the release of digestive enzymes by the sperm acrosomes, letting the sperm digest a path through the zona pellucida to the oocyte. The acrosome reaction also exposes egg binding proteins which are necessary for binding to the plasma membrane. The two membranes can now fuse, and the sperm delivers its cargo into the cytoplasm.

Inside zona pellucida, a narrow fluid fills the space outside the egg cell membrane. The first sperm to make contact, will fertilised the egg. The sperm attaches, the outer membrane diffuses, and the egg pulls the sperm inside. This causes changes in the egg membrane to prevent other sperm from attaching to it. Afterwards, the eggs release chemicals to push other sperm away from the egg, creating an impenetrable fertilization membrane and no sperm can attach anymore to zona pellucida.

Finally, the male genetic material spreads out, forming the pronucleus around it. Similarly, female genetic material is stimulated by the fusion of the sperm with the egg and finishes dividing. PLC-zeta is necessary to activate the egg by triggering an increase in intracellular calcium, activating specific proteins. Microtubules pull both female and male pronucleus toward each other and the two sets of chromosomes join together. Fertilisation is complete as genetic code arises, determining gender, hair and eye colour, and hundreds of other characteristics. The new single cell is called a zygote.

3. You are a script writer for the next superspy James Bond (007) film: 'Yet Another Unpleasant Way to Die'. In one scene, in a Cold War bunker, the eponymous hero, 007, is forced to take a cyanide pill by the latest nemesis. Luckily, his two colleagues, Q and Moneypenny arrive in time to administer the antidote. Provide some punchy (short sentences) dialogue (i.e., a conversation) that allows Q and Moneypenny to explain what the cyanide is doing to his mitochondria and how the antidote will save him.

Cold war bunker, 2030

James Bond has lost the fight. He is on the floor in the middle of the bunker and his last nemesis is about to kill him. 007 has no other option than to take the cyanide pill.

(007)

- You will never catch me alive!

James Bond grabs the box he has been hiding in his pocket in a quick movement and takes the cyanide pill.

(Nemesis)

- No one will know you killed yourself and the world will thank me for your death.

Laughing scandalously, the bad guy leaves the room and disappears. Q and Moneypenny watch him exit the bunker behind a stone and enter the small space as soon as they believe they could not be seen. A faint bitter smell of almonds pervaded the air.

(Moneypenny)

- Oh, no! Bond is dead.

(Q)

- Look, the cyanide box pill is empty.

(Moneypenny)

- He took the pill. We have less than three minutes at most to find the antidote.

(Q)

- This is a cold war bunker; we should be able to find a cold war era kit hiding somewhere. Let's take a look around.

(Moneypenny)

- Here!

Moneypenny gets the kit and opens it. They find four different pills with each label: sodium nitrile, sodium thiosulfate, and amyl nitrite, and hydroxocobalamin.

(Q)

- We should do something now! He will die very soon.

Hastily, Moneypenny puts hydroxocobalamin on James's mouth and obligates him to accept it.

(Q)

- What is that? How do we know it will save him?

(Moneypenny)

- It is hydroxocobalamin. It reacts with cyanide by binding tightly to cyanide ions. Each cyanide ion reacts then with a molecule of hydroxocobalamin to form cyanocobalamin, a non-toxic compound.

(Q)

- Does this mean that he will no longer have cyanide in his organism?

(Moneypenny)

- Exactly, the antidote decrease gradually the effects of cyanide and it excretes the cyanocobalamin using the urine.

(Q)

- Those are good news! I thought the hydroxocobalamin could only be injected into a vein. Good thing that we found a pill in the kit.

  They both look at 007 lying on the floor. Worry starts to rush through them when he doesn't start moving.

(Moneypenny)

- He is not waking up. I am getting worried; the pill is so deadly.

(Q)

- Well, the fact that the cyanide prevents the mitochondria from completing the electron transport chain of aerobic cellular respiration doesn't help to calm my nerves either.

(Moneypenny)

- I know that the last enzyme in the electron transport chain is the cytochrome C oxidase, which has an iron atom.

(Q)

- That is exactly where the molecule of cyanide binds. This transforms the enzyme to an irreversible inhibitor and prevents the oxygen flow.

(Moneypenny)

- But if the cyanide blocks the chain and oxygen cannot attach electrons to the end of the chain, how can the new electrons be added from NADH at the beginning of the chain?

(Q)

- They can't. Under those conditions, proton pumping stops and the proton concentrations on both sides of the membrane become balanced.

James Bond start to move slowly and quietly.

(Moneypenny)

- And of course, this will stop the proton flow through the ATP-generating enzyme, preventing the production of more ATP. Do you know what will happen if the cell does not create ATP?

(Q)

- Well, because the mitochondria are unable to create energy in form of ATP without oxygen, then each cell begins to die when they don't have the proper energy to maintain their basic functions.

(Moneypenny)

- But the glycolysis also produces ATP, and without using oxygen.

(Q)

- Unfortunately, cells cannot live long on the small amount of ATP produced by glycolysis alone.

(Moneypenny)

- So, this means that the victim dies when every cell of their body that requires ATP to survive consume all its energy.

(Q)

- Precisely, this is the reason why we had to be quickly to administrate the antidote.

(007)

- Are you two done playing biomedical scientist? I wouldn't mind some help getting up and going very far away from this bunker. The floor is cold, and I need to pee.

(Q)

- Oh my god! You are alive! I almost thought you were going to die.

(Moneypenny)

- Luckily, we found the kit and we knew what was going on. Let's get out of here before that crazy guy realise you are not dead.

END

4. Based on your knowledge of metabolism and inhibitors, and your experience in the lab, design an experiment to test the relative importance of glycolysis and oxidative phosphorylation for ATP generation in low oxidative, fast oxidative and fast glycolytic skeletal muscle fibres using metabolic inhibitors in vitro (using myofibres in cell culture).

The ATP source of fast glycolytic fibres is anaerobic glycolysis. They contain very few mitochondria and consequently, this type of cells has a low supply of oxygen. Fast glycolytic skeletal muscle fibres break down ATP quickly. On the other hand, oxidative skeletal muscle fibres have aerobic metabolism and a high supply of oxygen. The slow oxidative fibres break down ATP slowly, unlike fast oxidative fibres which break down ATP quickly, producing an elevated amount of tension with a slow fatigue.

When inhibiting a metabolic process, the cell will not be able to continue their basic functions. The metabolic inhibitors are deoxyglucose for inhibiting glycolysis and oligomycin to block ATP synthase.