Homeostasis Worksheet 3

1

Stimulus-secretion coupling is the phenomenon whereby upon certain stimulation, a cell such as a neurone or endocrine tissue releases, or secretes, a substance extracellularly, such as a neurotransmitter or a hormone. It is noticed, for example, that if an action potential passes along a neurone, at the terminal end of the axon there is the release of a neurotransmitter, such as acetylcholine. However, it is not the stimulus of the voltage change in the membrane that directly causes the secretion. They are coupled by an intermediate step which involves calcium. Upon stimulation of the membrane by an action potential, voltage gated calcium channels are forced to open. This results in an increase in calcium cation concentration in the cell. It is the increase in the intracellular concentration of calcium that causes the vesicles to translocate to the membrane and fuse, releasing the neurotransmitter to the external.

2

Activation (or excitation) – contraction coupling is the phenomenon whereby upon the neurotransmitter passing to the postsynaptic membrane and causing an action potential to be initiated, the muscle undergoes contraction. This process is once again coupled by the actions of calcium ions in the sarcoplasm. Within the cell there are stores of calcium within sarcoplasmic reticular cisternae vesicles. Upon activation by an action potential, the voltage change in the membrane causes large numbers of calcium channels through the membrane of the cisternae to open. They remain open for a few ms during which the calcium concentration of the cytoplasm increases. The calcium ions that are released diffuse to the adjacent myofibrils, where they bind strongly with troponin C and this in turn elicits the muscle contraction. The calcium is resituated into the vesicles by active transport after contraction.

3

When the extracellular concentration of calcium ions falls below normal, the nervous system becomes increasingly more excitable, because this causes increased neuronal permeability to sodium ions, allowing easy initiation of action potentials. At about 50% below normal, the peripheral nerve fibres become so excitable that they begin to discharge spontaneously, initiating nerve impulses that cause tetanic muscle contraction. Consequently, hypocalcaemia causes tetany.

4

It was hypothesised that upon stimulation of a neurone that at the terminal end, there was the release chemicals, resulting in chemical transmission. The two people mainly responsible for work in this area are Dale and Loewi. Dale investigated the effects of acetylcholine on body functions. He found that it inhibited heart beat of frog, caused contractions of frog intestine muscles. He suggested that acetylcholine occurs naturally in the body, acting as an antagonist to adrenalin. He hypothesised that it was rapidly broken down by hydrolysis – explaining why it had never been isolated. The next stage came from Loewi. The heart can be inhibited by stimulation of the vagus nerve. Loewi found that the perfusion fluid from an inhibited heart would reduce the amplitude of the heart beat even in absence of stimulation by the vagus nerve. Perfusion fluid from a normal heart did not have this effect. This meant that stimulation of the vagus nerve resulted in the release of a chemical substance. He later showed that the chemical was in fact acetylcholine, proving that it did exist in the

body. The microelectrode experiments have consequently proved that acetylcholine is released from the presynaptic membrane in quanta, representing individual vesicles, each causing an mEPP, with the EPP being due to the accumulation of many. The electron microscope has also allowed the vesicles of acetylcholine to be observed, as well as their release upon stimulation. All of this evidence has allowed the chemical transmission hypothesis to be shown to be correct.

5

Immediately opposite the active zones where the quanta of a ACh are released can be found ACh receptors within the postsynaptic membrane. These consist of five subunits, all of which are transmembrane, creating a pore through which ions can pass. The pore is lined with negatively charged side groups which inhibits the movement of anions, but facilitates the movement of monovalent cations. The pore is opened by the binding of two ACh molecules, one to each of the alpha subunits. Upon opening, it is found that the membrane becomes permeable to both sodium and potassium. It is not exclusively permeable to just sodium, or just potassium, but is permeable to both. Using the Goldman equation, considering approximately equal permeability to both sodium and potassium, it is found that the membrane potential that results is about 0mV, which is observed.

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The time for a 50g mass to be lifted from a surface is greater than that required to lift a 5g mass. The reason for this is that the extra mass causes a little extra tension in the muscle. The result of this is that there is the requirement of a little extra shortening of the muscle, i.e., contraction, before the external load changes its position. This is also due to the force-velocity relationship. A skeletal muscle contracts extremely rapidly when it contracts against no load – to a state of full contraction in about 0.1 seconds. When loads are applied, the velocity of contraction becomes progressively less as the load increases. When the load increases to equal the maximum force that the muscle can exert, the velocity of contraction becomes zero and no contraction occurs, despite activation of the muscle. This decreasing velocity with load is caused by the fact that a load on a contracting muscle is a reverse force which opposes the contractile force caused by muscle contraction. Therefore the net force available to cause velocity of shortening is correspondingly reduced. This also helps to explain the previous point.

9

A disorder of neuromuscular transmission is Myasthenia Gravis. It occurs in about 1 in every 20,000 people. It causes paralysis because of inability of the neuromuscular junctions to transmit signals from the nerve fibres to the muscle fibres. Antibodies that attack the acetylcholine gated receptors have been found in the blood of most patients of the disease. Therefore it is believed that myasthenia gravis is an autoimmune disease. What happens is that the endplate potentials that occur in the muscle fibres are too weak to stimulate the muscle fibres – because progressive reduction in the number of functioning AChR's. If the disease is intense enough paralysis, especially of the respiratory muscles, can kill the patient.

10

The general mechanism of muscle contraction is as follows:

1. An action potential travels along a motor nerve to its endings on muscle fibres
2. At the ending, the nerve secretes a small amount of the neurotransmitter substance, acetylcholine
3. The ACh acts on a local area of the muscle fibre membrane to open multiple AChR's within the membrane of the postsynaptic membrane
4. opening of the AChR's allows sodium to flow to the interior of the muscle fibre membrane which activates an action potential in the muscle fibre
5. The action potential travels along the muscle fibre membrane in the same way that action potentials travel along the nerve membrane
6. The action potential depolarises that muscle membrane, and much of the action potential electricity also travels deeply within the muscle fibre. Here, it causes the sarcoplasmic reticulum to release large quantities of calcium ions that are stored within it.
7. The calcium ions initiate attractive forces between the actin and myosin filaments causing them to slide alongside each other, which is the contractile process
8. After a fraction of a second, the calcium ions are pumped back into the sarcoplasmic reticulum by a membrane pump, and they remain stored until a

new muscle action potential comes along. The removal of the calcium ions from the myofibrils causes muscle contraction to cease – and relaxation occurs

11

Several hours after death, all the muscles of the body go into a state of contracture called ‘rigor mortis’ that is, the muscles contract and become rigid even without action potentials. This rigidity is caused by the loss of all the ATP, which is required to cause separation of the cross bridges from the actin filaments during the relaxation process. The muscles remain in rigor until the muscle proteins are destroyed later by enzymes released from lysozymes some 15 – 20 hours later

12

Preload contraction is one in which the muscle is loaded in the resting state and then stimulated (not used much since the initial length of the muscle will vary with different loads). I.e, it is the tension on the muscle when it begins to contract. After loaded contraction is where the muscle is not loaded at rest, but must lift a load in order to shorten. i.e., it is the load against which the muscle exerts its contractile force.