"Compare the mechanisms producing action potentials at a sensory receptor and at a motor neuron."

In all **sensory receptors** the stimulus causes a change in membrane permeability, causing a generator potential. However, many sensory receptors - photoreceptors, cochlear hair cells and vestibular hair cells - do not produce action potentials as a result, but have their generator potential sensed by a sensory neuron via a synapse. The other classes of receptor do produce action potentials, and by diverse methods.

Olfactory receptors respond via selective surface receptors to odorants in the local environment, perhaps bound to an olfactory binding protein in the mucous layer. The mechanisms involved are not fully understood but one method by which the cell can respond involves cyclic nucleotide second messengers. The ligated receptor may trigger a stimulatory G-protein (known as G_{olf}) which can activate an adenylate cyclase. This causes a rise in the intracellular cAMP concentration. The change in membrane potential is caused by the opening of sodium channels and, unusually, the channel is directly gated by cAMP and cGMP. Other mechanisms of transduction may exist; a route involving IP_3 is a candidate. However, once the sodium channels open an action potential is fired in the classical way if the depolarisation produced is sufficient to bring the cell to threshold. This process causes the phenomenon by which increased odorant concentration increases the rate of action potential firing - [cAMP] is directly responsible (fig. 1).

Gustatory receptors are capable of generating action potentials in the manner described for olfactory receptors, but during normal physiological responses the signals it generates are thought to be subthreshold, so an action potential never fires and the graded receptor potential is responsible for transmitter release onto the afferent fibre synapsing with the cell. This is feasible because the cell is very short, with afferent fibres synapsing with it at its cell body. The short distance allows passive spread of the depolarisation from the area at the other end of the cell where the tasty molecule is sensed. Olfactory cells could not do this, being far too long for passive spread to be sufficiently reliable and sensitive (and sensitivity is a key feature of the olfactory system, allowing long-range detection of odours).

Mechanoreceptors come in various shapes and sizes. Most are surrounded by structures that modify the sensitivity or the time-course of the receptor's response, but all seem to be based on channels which are linked to the cortical cytoskeleton and which are opened in response to mechanical deformation of the cytoskeleton. They are relatively non-selective cation channels (reversal potential around 0mV; they admit $Na^+/K^+/Ca^{2+}$). This results in the generator potential, which will trigger conventional action potentials via voltage-gated sodium channels. However, they may adapt by various methods (even as naked nerve fibres) including the inactivation of Na^+/Ca^{2+} channels or activation of a Ca^{2+}-dependent K^+ channel; by this means they may fail to fire action potentials in the face of a persistent stimulus.

Thermoreceptors fall into two categories: warm and cold receptors. Each class innervates the skin in a punctate fashion (so an area about 1mm in diameter may be a 'cold spot' or a 'warmth spot') and they respond to cold or to warmth in the physiological range (fig. 2). How local changes in temperature are rapidly transduced into variations in ion channel permeability is uncertain. However, a result of the mechanism is that cold receptors fire when they are very hot, too; and thermoreceptors are quite highly variable in their response curves.

Nociceptors detect tissue damage. They can detect mechanical and thermal stimuli when they becomes damaging, and also respond to some chemical mediators of inflammation (particularly histamine and bradykinin). They are subdivided according to their response: *thermal* or *mechanical nociceptors* obviously respond to high temperature or hard shocks; *polymodal nociceptors* respond to a wide variety of high-intensity mechanical, chemical or thermal (hot or cold) stimuli. The mechanism by which they transduce is unknown, though it seems that the transduction mechanism for each type of stimulus is distinct, because the threshold of a polymodal receptor to one submodality of tissue damage can be altered without affecting its threshold for others. It is likely, though, that the response to chemicals made by the organism (such as bradykinin) is via simple chemical receptor; and it has been suggested that a rise in extracellular K^+ as a result of tissue damage may depolarise the cell.

Motor neurons, by contrast, do not transduce complex forms of energy. They respond to multiple synaptic inputs from other neurons and integrate that input to provide a single output in the form of a frequency-modulated chain of action potentials.

Postsynaptic receptors fall into three main classes (fig. 3). There are ligand-gated ion channels, which may be excitatory (such as one of the glutamate receptors, passing Na^+/K^+) or inhibitory (such as the glycine receptor, passing Cl^-). These show a very rapid response, and may adapt by inactivating or by being sequestrated. Then there are receptors which activate a G-protein system (stimulatory or inhibitory) which then affects the state of an ion channel (which itself may depolarize or hyperpolarize the cell when opened). This system is slightly slower and longer-lasting, and has more potential to be interfered with (such as by uncoupling the receptor from the channel). Finally, there are receptors which act via a second messenger system, such as cAMP or IP_3/DAG, to affect the channel in a slower but more permanent way.

Neurotransmitters, too, fall into several classes: there are the small molecule transmitters, consisting of ACh, the catecholamines, several amino acids and 5-HT; and there are the neuropeptides, of which there are many. The small transmitters tend to have specific mechanisms for their removal and are released first from presynaptic terminals; they tend to act in a localized manner. The peptides are released upon more vigorous and prolonged stimulation of the presynaptic neuron; they are not released quite so specifically into the synaptic cleft, and tend to "float around" having more general and long-term effects on surrounding cells before they are removed by rather non-specific peptide uptake systems. ACh predominates in the motor system.

Crucial to the integration of synaptic input from these various synapses that may impinge upon a motor neuron is the fact that one region of it - the axon hillock - has the lowest threshold for initiation of an AP of any point on the cell. This is due to the high density of voltage-gated Na^+ channels. It will fire a propagated AP if it is depolarized by only 10mV (to -55mV, compared with -35mV for most of the rest of the cell). No one postsynaptic potential is capable of causing the motor neuron to fire, though: there may be 10,000 inputs to the cell, and it is the integrated response to these, the "summed" potential, that determines the firing frequency of the neuron.

Each synapse may contribute an excitatory or inhibitory postsynaptic potential, of up to 0.4mV at an excitatory synapse. This then spreads along the membrane electrotonically in all directions, and thus may influence the potential at the axon hillock. However, not all synapses are created equal. Axosomatic synapses (onto the cell body) have a greater influence on the axon hillock potential - being nearer - than axodendritic synapses, for example. Furthermore, inhibitory synapses create an IPSP by opening Cl^- channels. Normally, the chloride current through them is not great as the electrochemical gradient for chloride to move is small; thus the membrane potential is hardly changed. However, in the presence of an EPSP and depolarization, much more Cl^- will flow through the channel. In this way, known as *shunting*, a small IPSP can short-circuit EPSPs greater in magnitude, provided they are located closer to the cell body.

Thus it is found that synapses on dendritic spines tend to be excitatory; synapses on cell bodies tend to be inhibitory (an inhibitory impulse would have little effect far out on a dendrite!) and synapses on axon terminals tend to be modulatory - these last have no direct effect on the trigger zone of the cell but modulate the amount of transmitter it releases.

The motor neuron, in addition to the spatial summation of incoming impulses discussed, carries out *temporal summation* of its inputs. An EPSP will last about 3ms, with its rate of electrotonic decay depending on the time constant for the membrane (just as the decay in space depends upon its space constant). Should a second EPSP arrive sufficiently soon after the first, the two may sum temporally to create a greater depolarisation than either would produce together. Similarly, an IPSP could 'wipe out' an EPSP that had arrived shortly before.

Decision-making neurons such as the motor neuron also show *synaptic plasticity*: the response of the neuron depends on the time-course and nature of the input to it. Facilitation, potentiation and depression are all shown on fig. 4. Facilitation may be due to simple Ca^{2+} build-up, but may be due to more complex modification of channel activity to prolong the AP, increase $[Ca^{2+}]$ and thus enhance transmitter release. Potentiation may also be by several methods, but the motor neuron is not the best example of its workings. Depression of the release of neurotransmitter (as occurs in habituation of a reflex to a stimulus) is not fully understood; part of the decrease is thought to be due to inactivation of a calcium channel in the presynaptic terminal, so that less Ca^{2+} enters the terminal to cause transmitter release. In addition - and probably more importantly - habituation decreases the ability of transmitter vesicles to be mobilised for release.

Thus unlike sensory receptors, which are the point at which the outside world is 'mapped' to the neuronal code of frequency-modulated action potentials, a motor neuron has a tremendous capacity for integration of information, and a great deal of diverse information impinging on it. It has the basic

decision-making capacities of a neuron, and its output is a very complex function of its input; its full workings are far from understood.

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