How do drugs interact with receptors biology essay

Illustrate with named drug examples. Receptors are highly important in cell function as they allow communication between a cell and its neighbours and controls the way a cell functions with stimuli or depression, usually from the central nervous system via the brain and spinal cord (Patrick, 2005). The nerves that communicate with their respective cells do not connect directly to their target cells, and there has to be some way of carrying their message across a gap of only 100 Å, and this is achieved by the release of chemical messengers from the nerve cell to interact with receptors in the target cell membrane (Patrick, 2005). These receptors are protein molecules, usually embedded in the cell membrane, with a certain area of this protein on the outside of the cell which is able to bind this chemical messenger due to the proteins structure. This binding of the chemical messenger leads to the activation of the receptor which leads to the desired effect which can occur via a number of methods (Katzung, 2001). When this process goes wrong, for example of too much or not enough messengers are released, then disease states can occur, with Parkinson’s disease, depression and psychosis being among many diseases thought to be resulting from this sort of pathophysiology (Patrick, 2005). When this occurs, drugs, which may be defined as ‘ any substance that brings about a change in biological function through its chemical actions’ (Katzung, 2001), can be used to have an effect on the desired receptors to increase or decrease their activity, and hopefully restore the balance as close to the physiological normal as possible. In this essay, I shall first discuss how drugs can have their effect on receptors and will then go on to discuss how these drugs work on different types of receptors to treat disease.

There are many, many different receptors in the body with different shapes, sizes, regulating factors and functions. These can be classified into five main classes: (i) ligand gated ion channels, (ii) intracellular receptors for lipid soluble agents, (iii) ligand regulated transmembrane enzymes, (iv) cytokine receptors, and (v) G proteins and second messengers (Patrick, 2005). Throughout the essay, I will try to explain how drugs interact with receptors and how this can affect their function. I will also try and use a balanced coverage of the above receptor classes as examples when describing how drugs can affect a receptors function.

Firstly, a drug may be used to mimic the action of a natural chemical messenger to activate the receptor and cause an increase of activity at that cell, for example, initiating muscle movement or secretion of a hormone (Patrick, 2005). These types of drugs are called agonists, but their function at a receptor depends on a number of factors that need to be considered when designing new drugs. One requirement is that the drug has to have the correct binding groups, so that the required number of interactions, for example, ionic bonding, hydrogen bonding, van der Waals interactions etc.; can be made between the drug and the receptor, and that these interactions are strong enough to stimulate the receptor, but not too strong so that the drug does not leave the receptor after binding (Katzung, 2001). The drug must also have the correct size and shape to fit into the receptor binding site and allow these interactions to occur. If the drug is too small, the drug will not be able to sufficiently form the required interactions with the receptor, and if too big, the drug will not be able to fit into the binding site at all. This has become a lot easier since the protein structures of many receptors, and

their binding sites, have been identified via genetic engineering, computer based molecular modeling and X ray crystallography, allowing for the design of specific drugs to fit these binding sites (Patrick, 2005). In terms of how the chemical messengers and drugs have their effect on the receptor to activate it, it is thought that the binding interactions of the messenger molecule cause the receptor to change shape. As an example, if a receptor had three binding sites, when the agonist reaches the receptor, it may only interact with two of the three required interactions. In order for the third interaction to take place, the protein must undergo a conformational change, and with this change, the receptor will become activated and cause a change in the cells activity (Katzung, 2001). This is a very simplified view and in reality, the conformational changes needed to open a channel such as an ion channel are complex and often, the lock gate is not in close proximity to the receptor binding site, but the same ideas are common to both.

A very common prescribed agonist is Salbutamol, a selective β-2 adrenergic receptor agonist, in the treatment of asthma (Waldeck, 2002). This is a G protein coupled receptor which is expressed mainly in the lungs in the alveolar walls. When this receptor is activated, levels of intracellular cyclic adenosine monophosphate (cAMP) via G-protein activation of adenyl cyclase. The increase in cAMP in the cells influences cAMP dependant protein kinases which contribute to regulation of muscle tone and reduce free calcium ions on the cell by stopping their influx from outside the cell and also their release from intracellular stores (Kroeze, 2003). This then results in relaxation of the central and peripheral airway smooth muscle and therefore bronchodilation (Sears, 2005). Benzodiazepines can be used as

anticonvulsants for treatment of epileptic seizures and work by acting as agonists of the GABAA receptor in the central nervous system. These work by binding to a specific benzodiazepine binding site at the interface of the α and γ subunits which is present on a subset of GABAA receptors (Treiman, 2001). When a benzodiazepine binds to this site, it increases the affinity of the receptor protein to bind GABA, and therefore increases the chance that the channel will open. With the channel more likely to be open, this allows the flow of chloride ions through the channel and therefore hyperpolarizes the membrane and makes the associated neuron less likely to potentiate an action potential, hence the drugs sedative properties (Treiman, 2001).

Agonists are a good therapeutics agent for when there is not enough chemical messenger in a system, but what if there is too much being produced? In this situation, an antagonist is used. An antagonist is a drug that can bind to a receptor binding site but does not produce a functional conformational change like an agonist, or if it does change the shape of the receptor protein, it does so in a way in which the desired effect on the cell does not occur (Patrick, 2005). These are called competitive antagonists as they compete with the natural chemical messenger for the receptor binding site and therefore block the action of the messenger, preventing it from having its effect. Competitive agonists are usually designed to bind to the binding site more strongly, so enhancing its anagonistic effects (Patrick, 2005). Antagonists can also work on the receptors but not actually at the binding site. These are termed allosteric antagonists with the drug binding to a different part of the receptor and the interactions involved may then distort the shape of the receptor in such a way that the natural chemical transmitter

cannot bind as the binding site will no longer be compatible. This is an example of non-competitive antagonism as the drug is not competing with the natural chemical messenger for the same binding site (Katzung, 2001). An example of an ion channel antagonist is Amlodipine, which has its effect on voltage gated L-type (slowly inactivating) calcium channels (Abernethy, 1999). This drug is used for a variety of cardiovascular diseases, for example, hypertension and angina pectoris (Abernethy, 1999). With the calcium channels blocked, there is less influx of calcium into the cell, and in smooth muscle cells, this decrease in the intracellular messenger leads to a reduction in muscle contraction. This means that vasodilation takes place and leads to a decrease in blood pressure (Abernethy, 1999).

Sometimes, a drug is discovered that cannot be classed as a pure agonist or a pure antagonist, its action involves it having some effect on a receptor to produce its activation, but not as much as would be seen with an agonist. These are termed partial agonists. There are many theories into how these work because it does seem strange that an agonist can only work ‘ partially’. One such explanation is that when the partial agonist binds to the binding site, it does form the required interactions to produce a conformational change, but this change is not exactly the same as a pure agonist, and so may only activate the channel partially, for example, by only partly opening an ion channel (Patrick, 2005). Another theory involves the partial agonist being able to bind to the receptor in more than one place, so one method of binding would produce an agonist effect and the other an antagonist effect. This balance between the two would result in only a proportion of the receptors being activated, hence, the partial antagonistic effect (Katzung,

2001). An example of a partial agonist is clozapine which is classified as an atypical antipsychotic and can be used for its anti-depressive and anti-anxiolytic effects in some patients. Along with effecting dopamine receptors, it also binds to serotonergic receptors, particularly the 5-HT1A receptor, to which it has its partial agonist effect (Meltzer, 1989).

There is another way drugs can interact with receptors and this is in the form of an inverse agonist. These work on the principle that some receptors have constitutive activity, for example the GABA receptors, in which they are active at all times, regardless of signals they are receiving, so can be active even without the presence of a natural chemical messenger or an agonist (Patrick, 2005). This can even be true when an antagonist is present as the antagonist has the same binding affinity to both the active and inactive receptors, so there is no change in biological activity because the active receptor remains active. An inverse agonist has the effect of binding to the receptors and stabilising them in the inactive state, so will reduce the number of active receptors that are functioning, so will almost prevent any receptors from being active as it even stops the constitutive activity, so has a ‘ negative efficacy’ (Patrick, 2005). Figure 1 represents a diagrammatical representation of this (Lambert, 2004). Cimetidine, a H2 receptor inverse agonist, is used for the treatment of dyspepsia and peptic ulcers (Wallmark, 1983). It works by blocking the binding of histamine to the receptor on the parietal cells which reduces the amount of acid that is secreted by these cells into the stomach (Wallmark, 1983). The parietal cells secrete more acid when stimulated by histamine release after a meal, but also have a

constitutive activity, which the inverse agonist also suppresses (Wallmark, 1983).

Fig. 1 Graphical representation of the negative effect that inverse agonists have on receptors when compared to an antagonist and an agonist (Lambert, 2004).

In conclusion, there is many ways in which drugs can act on receptors to modify their effect and this can be utilised for treating disease when a system goes out of balance. As mentioned previously, huge advancements have been made since more is now known regarding the structure of receptors and their binding sites. In the future, with more knowledge acquired in this field, further drugs can be manufactured which can be much more specific to their respective receptor and so can produce specific desired effects. This is of particular importance in conditions affecting the brain as disorders such as depression, schizophrenia and Parkinson’s disease are associated with an imbalance in neurotransmitters and improvements in the drugs available to us to treat such conditions will benefit millions of people all around the world.