Prescribing for Paramedics: Pharmacodynamics

Introduction

In continuing the theme of *Paramedic Prescribing*, this article will explore the nature of drug actions that occur within the body. An understanding of these principles allows the paramedic to make an informed decision on the medicines that may be offered, the likely outcomes and the possible risks. Often considered a complex subject, this article aims to present a set of principles that the reader can apply to almost all drugs that one may encounter. Where appropriate, relevant case studies have been included to support theory and provide contextual examples.

Drug action

Many drugs exert their effect on the body via an action on cells. The net effect of this can be to increase or reduce an action (*agonist*), prevent an action altogether (*antagonist*) or to enhance an existing process (*allosteric* modulation). Drugs can do this a number of ways, but the most common methods are to chemically bind to the surface of a cell or in the case of steroids, simply pass through the cell wall. Before discussing these methods in detail, we must acknowledge that these processes occur naturally in the body; our pharmacological interventions simply mimic the endogenous neurotransmitter or hormone. The importance of these endogenous chemicals cannot be understated. Indeed, before acetylcholine was the first neurotransmitter to be identified (Dale, 1914), synapses were widely considered to occur via an electrical process. The matter was largely put to rest after Loewi (1921) carried out his well-known *frog* experiment which initially came to him in a dream.

G-Protein coupling

Widely regarded as the largest family of drug targets, G-protein coupled receptors (GPCRs) frequently reveal the way in which drugs interact (Zhao et al, 2016).

When a drug binds to a receptor site the physiochemical properties of that cell change; this is known as a *conformational* change. Next the alpha sub unit of the G-protein dissociates and activates an enzyme which catalyses a further chemical reaction. The subsequent product is a second messenger molecule able to send signals to the body from within the cell (Figure 1). Taking adrenaline as an example, the second messenger signals could increase blood flow to skeletal muscle, increase glucose production, cause peripheral vasoconstriction or even cause bronchodilation. The effect would be largely dependent on dose and route. In this example, the second messenger molecule would be cyclic adenosine monophosphate (cAMP). It is important to note that cAMP is an intracellular signal transducer and doesn't itself represent a body that exits the cell.

Alternatively, once dissociated, the alpha sub unit could block or open specific ion channels (Figure 1). The result here would be to prevent depolarisation, prolong repolarisation, raise or lower threshold potentials. The affects would depend on location of these particular cells and the method of administration. A good example here would be lidocaine: local administration would block sodium

channels and prevent (slow) depolarisation of nerve cells and hence provide local anaesthesia. However, when administered IV, lidocaine blocks myocardial sodium channels and depresses myocardial contractility in VT (Mccann, 2000).

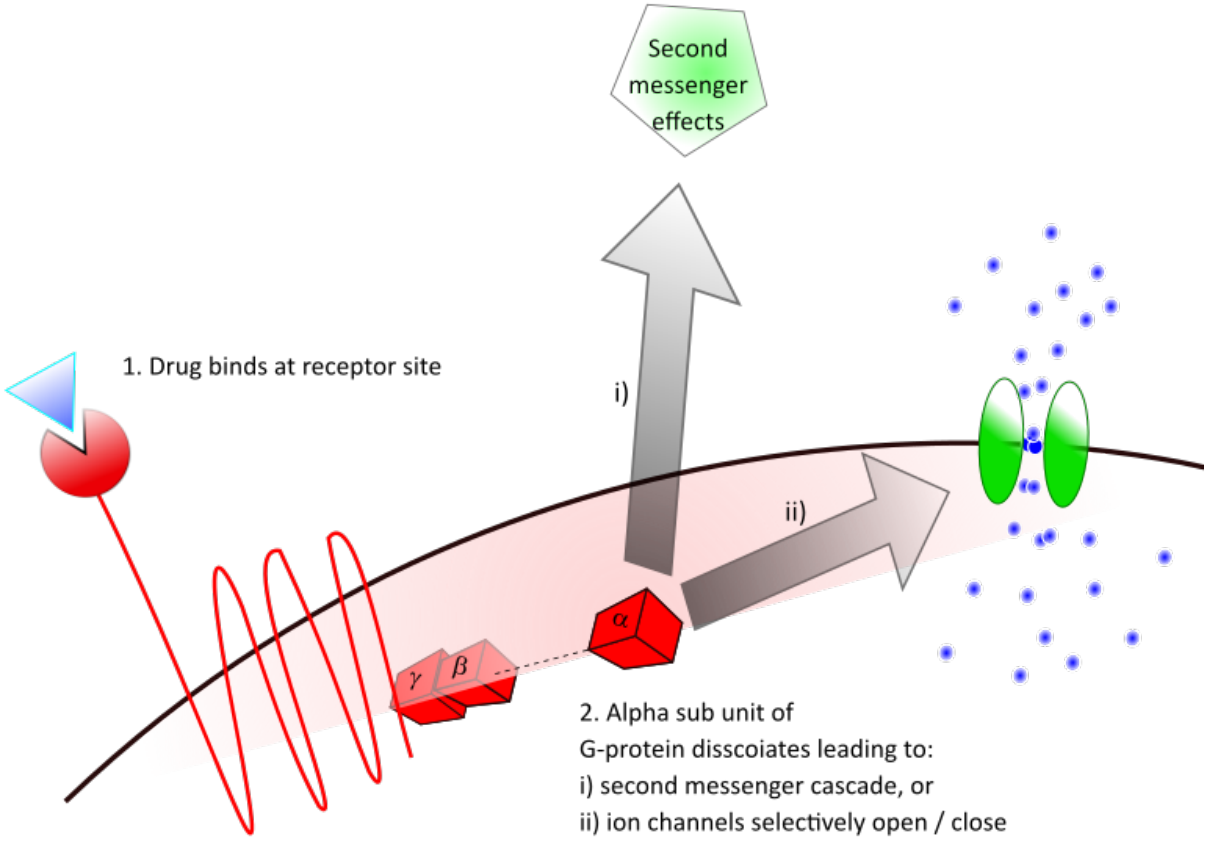

Figure 1. GPCR interaction leading to i) second messenger, or ii) changes to ion channel

Before moving on, we should consider the strength of the interaction between drug and receptor site and the concentration (amount of drug available). For a therapeutic result the dose of a drug should be sufficient that a significant number of receptor sites are exposed to the drug. Too little and there will be little or no physiological action, too much and we risk toxicity or overdose.

When a number of drugs, hormones or neurotransmitters are available to a receptor site it is not simply a case of *first come, first served*… the receptor site will selectively bind to the molecule with the most preferable chemical properties. These properties will be a specific combination of chemical properties including structure, polarity (as well as how the charge may be distributed across the molecule), pH, solubility, etc. These properties refer to the *affinity* between drug and receptor and they allow for a more favourable drug to present itself and allow for displacement due to a greater

affinity. A good example of this is Naloxone which is known as a *competitive antagonist*; since it has a greater affinity to opiate receptor sites it will displace drugs (heroin, morphine, *etc*) which are already bound to receptor sites. The same chemical properties mentioned are also responsible for the *selectivity* of a drug: whether a drug will prefer a particular receptor site or will happily bind to a number of different subtypes. Propranolol, a non-selective beta blocker which may be prescribed for arrythmias should be introduced cautiously in patients with a history obstructive airways disease (BNF). Such patients are likely to be on beta-agonist inhalers (salbutamol) and in the presence of propranolol, the beta 2 receptor sites may well be blocked when the inhaler is required.

Steroid hormone receptors

Where G-protein receptor coupling occurs on the surface of a cell, steroids posses a unique ability to bind within cells. Steroids are able to diffuse across the plasma membrane of a cell due to their lipophilic nature, this is due to their hydrocarbon skeleton. Steroids have very small electronegativity values as bond lengths are short and the electrons within are shared (relatively) evenly, as a result they have a very small dipole moment (charge). Once through the plasma membrane the steroids can access receptor sites in the cytoplasm or the nucleus.

When a steroid enters a cell and binds to a receptor site the ensuing conformational change results in an interaction with cell DNA. The outcome is usually an altering of gene expression (specifically transcription and/or translation). Once the DNA of a cell has been infiltrated, a wide array of biological processes can be manipulated (Sever & Glass, 2016).

Prednisolone, a commonly prescribed steroid in cases of COPD exacerbation will bind to cytoplasmic receptors and modify cell DNA synthesis. After binding to the glucocorticoid receptors, the inflammatory cells and mediators are inhibited thus: with the synthesis of anti-inflammatory proteins as well as blocking the transcription of inflammatory genes. Following the suppression of these inflammatory processes, respiratory function can improve.

Transporter / Carrier molecules

Many bodily functions that are controlled by neurotransmitter release use a method of *reuptake* to moderate effects. These processes are controlled by enzymes which are sometimes assisted by transporter molecules. Without these actions the neurotransmitters would retain high concentrations in the synapse and lead to toxicity. An astute method of therapeutic modification involves the inhibition of said enzyme; this allows for a higher concentration of the neurotransmitter to be available to bind to receptor sites and maintain a physiological action. Fluoxetine, a commonly prescribed antidepressant is a class of selective serotonin reuptake inhibitor (SSRI) which acts by blocking the serotonin transporter (SERT) (Peng et al, 2014). Tricyclics such as amitriptyline block the *reuptake* of noradrenaline by inhibiting NAT (noradrenaline transporter) (Tatsumi et al, 1997). In the treatment of Parkinsonism, Amantadine maintains a concentration of dopamine by blocking its *reuptake* (Blanpied et al, 2005).

Antimicrobial pharmacology

The field of antibiotics is not one that can easily be presented here as the different classes all act in very different and specific ways. However, since they are among the most commonly prescribed, beta-lactams are provided as a case study.

All bacteria are prokaryotic, meaning their cells contain no distinct nucleus. Most biologically significant bacteria have a peptidoglycan layer outside their plasma membrane. This layer made of sugars and amino acids provides the target for many antibiotics. If the peptidoglycan layer can be destroyed or damaged, then the cell contents will be exposed and perish and the cell can no longer replicate. Within the peptidoglycan layer there are a number of proteins that link peptides together to create a mesh and envelope the cell. Penicillin comes a family of drugs known as beta-lactam antibiotics due to the unique beta-lactam ring which forms part of their structure.

Beta-lactam antibiotics selectively bind at the same locations where the peptides expect to form the links; by binding at these key locations the cell loses its structural integrity and the cell dies. If the concentration of the antibiotic is insufficient to completely eradicate the bacteria then resistance may occur. The most common method in this case is the synthesis of an enzyme (beta-lactamase) which binds with this class of antibiotic and renders them inactive (Lobanovska & Pilla 2017). The danger of misuse and the potential for resistance was first mentioned by Sir Alexander Fleming in his Nobel prize acceptance speech in 1945.

Conclusion

The principles of pharmacodynamics have been explored from the molecular to cellular level. The interactions of drugs based on chemical structure has also been discussed: whether this is by action at a receptor site on the surface of a cell, by passing through the cell membrane and influencing DNA, inhibiting the molecules which act as transporters or by simply destroying the wall of a cell and preventing replication. These are the generally accepted means by which most drugs will act and this knowledge allows us to adapt the mechanisms and apply them to other drugs one might come across as a prescriber.

References

Blanpied, T.A., Clarke, R.J. and Johnson, J.W., 2005. Amantadine inhibits NMDA receptors by accelerating channel closure during channel block. The Journal of neuroscience : the official journal of the Society for Neuroscience, [e-journal] 25 (13), pp.3312-3322. 10.1523/JNEUROSCI.4262-04.2005. <https://pubmed.ncbi.nlm.nih.gov/15800186 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6724906/>.

DALE, H.H., 1914. The action of certain esters and ethers of Choline, and their relation to Muscarine. Journal of Pharmacology and Experimental Therapeutics, [e-journal] 6 (2), pp.147-190. <http://jpet.aspetjournals.org/content/6/2/147.abstract>.

Lobanovska, M. and Pilla, G., 2017. Penicillin's Discovery and Antibiotic Resistance: Lessons for the Future? The Yale journal of biology and medicine, [e-journal] 90 (1), pp.135-145. <https://pubmed.ncbi.nlm.nih.gov/28356901 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5369031/>.

Loewi, O., 1921. Über humorale übertragbarkeit der Herznervenwirkung. Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere, [e-journal] 189 (1), pp.239-242. 10.1007/BF01738910. <https://doi.org/10.1007/BF01738910>.

Mccann, G., 2000. Pharmacological treatment of significant cardiac arrhythmias. British journal of sports medicine, [e-journal] 34 (5), pp.401-402. 10.1136/bjsm.34.5.401. <http://bjsm.bmj.com/content/34/5/401.abstract>.

Peng, L., Gu, L., Li, B. and Hertz, L., 2014. Fluoxetine and all other SSRIs are 5-HT2B Agonists - Importance for their Therapeutic Effects. Current neuropharmacology, [e-journal] 12 (4), pp.365-379. 10.2174/1570159X12666140828221720. <https://pubmed.ncbi.nlm.nih.gov/25342944 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4207076/>.

Sever, R. and Glass, C.K., 2013. Signaling by nuclear receptors. Cold Spring Harbor perspectives in biology, [e-journal] 5 (3), pp.a016709. 10.1101/cshperspect.a016709. <https://pubmed.ncbi.nlm.nih.gov/23457262 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3578364/>.

Tatsumi, M., Groshan, K., Blakely, R.D. and Richelson, E., 1997. Pharmacological profile of antidepressants and related compounds at human monoamine transporters : European Journal of Pharmacology.[e-]. 340 (2) pp.249-258. https://doi.org/10.1016/S0014-2999(97)01393-9. <http://www.sciencedirect.com/science/article/pii/S0014299997013939>.

Zhao, J., Deng, Y., Jiang, Z. and Qing, H., 2016. G Protein-Coupled Receptors (GPCRs) in Alzheimer's Disease: A Focus on BACE1 Related GPCRs. Frontiers in Aging Neuroscience, [e-journal] 8, pp.58. <https://www.frontiersin.org/article/10.3389/fnagi.2016.00058>.