The history of peptides as drugs biology essay

Peptides are compounds that are produced as a result of amide bond formation due to interaction between a carboxyl group of an amino acid and the amino group of another amino acid. Peptides, a regulator of most physiological processes and functions have found use therapeutically in areas like haematology, endocrinology and neurology. Generally peptides are classified based on the length of the residue, when a peptide contains less than 10 – 20 residues it is referred to as an oligopeptide, if it contains over 20 residues it is a polypeptide and if it contains more than 50 residues it is a protein (Edwards et al, 1999). There are structural differences beyond the primary sequence between peptides and proteins. Peptides of less than twenty (20) amino acid residues do not have a secondary structure which involves β sheets, β turns and α helixes. Peptides containing around fifty amino acid residues are more likely to possess secondary structure especially if they are stabilized by disulphide bonds, example of which is insulin. Tertiary structures are only found in proteins. Functions of peptides are basically dependent on the functional groups of the various amino acids, the functions of proteins are dependent on the on the maintenance of a precise 3D structure (Van der Walle, 2011)Humans suffer from diseases as a result of abnormalities in the production of polypeptides, carbohydrates and nucleic acids which can in turn be treated with the same class of compound that is responsible for their deficiencies. These polypeptides or carbohydrate can be used to treat diseases either by direct replacement, symptomatically which is basically a short term intervention that modifies the pathogenesis of the disease and prophylactically in the forms of vaccines that confer immunological protection against various pathogen (Bladon). Diseases like

dwarfism, gigantism and acromegaly occur as a result of hypothalamus-pituitary endocrine system dysfunction which causes insufficient or excessive production of the growth hormone, are usually treated either by growth hormone or analogues of growth hormone inhibitors. (Bladon, 2002)Peptide structure which is coded directly in the genome and synthesis of the body starts by the production of precursor proteins also known as preprohormone that contains the sequence of the peptide and the proteolytic enzymes that helps break off the active peptide (Rang & Dale, 2012). Insulin is yet to find a replacement in the treatment of diabetes mellitus, though research is still ongoing on better means of administration and analogues of insulin. Alterations to insulin molecule brought about the development of lispro insulin which is a shorter acting form of insulin. Its advantage is that it can be taken immediately before a meal due to its rapid absorption. New forms of insulin delivery has also been developed which include the inhaled, intranasal, rectal, buccal and sublingual preparations. These forms of insulin are mostly effective for individuals suffering from type II diabetes (non insulin dependent diabetes) as they do not need so much of the insulin. Some other peptides have been discovered in the treatment of diabetes mellitus. Peptides like islet amyloid, its precursor amylin and glucagon like peptide- 1 (GLP1) delay gastric emptying has been found useful in the treatment of diabetes. GLP1 suppresses glucagon levels and possess insulin releasing properties. Leptin, an adipose tissue peptide has roles in obesity and anorexia. Leptin causes a reduction in appetite and also increases the metabolic rate. Leptin could be used to treat obesity while its antagonist used in the treatment of anorexia. Octreotide is a longer acting

analogue of somatostatin and has found use in a lot of ailments like acromegaly, gastro enteropancreatic endocrine tumours , gastrointestinal tract bleeding, dumping syndrome, acute pancreatitisThere are different routes of administration for peptide drugs. The parenteral route is the most effective route for peptide delivery. It comprises of three routes; the intravenous, subcutaneous and intramuscular route. The intravenous is currently the most used route of administration for peptide drugs e. g. insulin. The non parenteral route which comprises of the oral, buccal, ocular, TABLE 1; SOME PEPTIDE DRUGS. DRUGUSEROUTEOxytocinInduction of labourInjectionInsulinDiabetesInjectionCyclosporineImmunosuppressionOralGrowth hormoneDwarfismInjectionSomatostatin, ocreotideAcromegalyIntranasal, injectionCaptoprilHypertensionOralADH, desmopressinDiabetesIntranasal, ionjectionTSH/TRHThyroid diseaseInjectionCalcitoninDisease of boneIntranasal, injectionGnRH analoguesInfertilityIntranasal, injectionAdapted from Rang and Dales pharmacology 7th edition

PRODUCTION OF PEPTIDE DRUGS.

Prior to the development of methods for the synthesis of peptides, they were solely obtained from biological sources, for example, insulin was obtained from pancreas of the slaughterhouse animals like pigs while blood was obtained from plasma. The main limitation to the use of proteins obtained from natural sources is the low yield obtained and the presence of pathogens and impurities. Impurities present in the peptide could render the peptide immunogenic thereby appearing as a foreign object to the body, this causes the production of antibodies to neutralise the effect of the administered

peptide. Peptide derived from animal sources frequently vary in amino acid sequence from that humans for example the C terminal of the B chain in human insulin is threonine while that of the pig is alanine. Presence of pathogens in peptides and proteins can lead to complications in therapy or could lead to development of another disease entirely. All these problems associated with the use of peptides as drugs could be combated with the use of peptides derived from other sources. (Blandon, 2002) Advancement in biotechnology has provided various avenues for the production of peptide and protein based drugs. Recombinant DNA technology (rDNA) can be used in the production of therapeutic peptides and proteins for example human growth hormone, insulin and interferon have been produced using rDNA. This is done by transferring of a specific human protein into a replicating vector DNA, the vector is then inserted into a host organism; the protein is then isolated and purified. This method can be used to effectively produce large amounts of peptides or proteins (Bladon, 2002, Pandey et al, 2009)Synthetic peptides used medicinally started with oxytocin and vasopressin which are cyclic nonapeptides possessing one disulphide bridge (Loffet, 2002). The production of peptides was very strenuous and not suited for long chain polypeptides. Bruce Merrifield in 1963 developed a new approach to peptide synthesis which is well suited for the production of long chain polypeptides; this method is known as the solid phase peptide synthesis (SPPS). The underlying concept of SPPS is the attachment of the first amino acid of the chain to a solid polymer with the aid of a covalent bond, then addition of succeeding amino acids in a step wise manner until you achieve the desired length. When the desired peptide length is attained, the solid support is then

removed (Merrifield, 1963). The development of solid phase peptide synthesis and better purification methods like high performance liquid chromatography (HPLC) has aided in the production of a lot of peptides (Loffet, 2002).

DRAWBACKS TO THE USE OF PEPTIDES.

Most peptide drugs are administered only through injections as a result of their short half- lives and rapid metabolism, but as a result of poor patient compliance and the inconveniences that can be caused especially if the drug is to be taken regularly as is the case with the multiply punctured diabetic a lot of research is currently on-going for other routes of administration like the buccal, intranasal, oral, pulmonary, transdermal, rectal and ocular (Pandey et al, 2009)Due to the big size of peptides they find it extremely difficult to cross the membranes and distribute in intracellular fluids, these poor delivery properties are compounded by their metabolic instability, non-lipophilic character and high hydrophilicity, these properties of the drugs impacts negatively on the bioavailability as the fraction of the administered drug getting to the bloodstream is about 1-2%. In systemic circulation, they quickly get cleared by glomerular filtration, enzymatic breakdown, immune system reaction and endocytosis. The half-life of peptides and proteins can be achieved by some little modifications. Peptides can undergo PEGylation in order to increase their half-life. PEGylation involves conjugating the peptide with poly ethylene glycol (PEG) which is highly water soluble, and possess high mobility in solution and low immunogenicity. This enhances the hydrophilicity of the molecule and it also makes it not recognisable by macrophages by preventing oponization. This method leads to steric

stabilization which aids the circulation of the drug for longer period of time. PEGylated drugs available in the market include interferon, asparaginase, granulocyte colony stimulating factor and tumour necrosis factor. PEGylation has been used in the production of liposomes of peptide drugs and nano particles (Pawan, 2010, Sato et al, 2006). Asides using PEG, peptides can also be modified in other ways to increase their half life and avoid breakdown by peptidases. Peptides can undergo N terminal (glycosylation, acetylation) or C terminal (amidation) adjustments and by utilising of unnatural amino acids like α and β amino trifluoromethyl at the labile sites of the peptides (Sato et al, 2006)A lot of research is being done to investigate other routes of administration of peptide drugs. The drugs can be administered locally thereby evading the systemic circulation; this also reduces the immune response of the compound and the breakdown by proteases. Non parenteral routes like oral, ocular, buccal, transdermal, vaginal, nasal and rectal are desired because of patience compliance and the frequency of injection needed to attain the desired concentration. Alternative routes help bypass first pass metabolism, provides sufficient absorption areas and there is a decreased presence of proteolytic enzymes (Dulal, 2010). Stabilization techniques involves a protein drug being secured in a carrier material either in entrapped form with in the matrix, encapsulated in a semi permeable membrane, adsorbed to the carrier or covalently attached to the carrier. The most common procedure for delivery through non parenteral routes is encapsulation, entrapment and covalent binding. Entrapment and encapsulation is based on two techniques like hydrogels and microspheres/nanocapsules and liposomes and micro emulsions. These

method should enable the drug overcome the adsorption barrier and have protective effect on enzymatic degradation example of an encapsulated drug is nafarelin (Dulal, 2010).