ADVANCED DELIVERY SYSTEMS FOR PEPTIDES AND PROTEINS - PHARMACEUTICAL CONSIDERATIONS

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Presently, a wide variety of routes of administration and delivery systems exists for drug substances, but by far the most popular approach is oral delivery where the drug is intended to be absorbed from the gastrointestinal tract. Injectable systems (that include implants), suppositories and transdermal devices, have a more limited place in current therapy. Some of these administration systems can be employed directly for the delivery of peptides and proteins, however, others cannot be used in their present form and will require extensive modification. In particular, the delivery of peptides and proteins via the gastrointestinal tract will be especially difficult because of the inherent instability of such materials and the poor permeability of the intestinal mucosa to high molecular weight substances. Indeed it can be claimed that the process of evolution, over many thousands of years, has resulted in the gastrointestinal tract being impermeable to large molecular weight molecules in the adult mammal and that serious immunological consequences could arise if such materials happened to be taken up intact. This point will be discussed further below. In future the less well known routes of administration, namely nasal, vaginal and buccal, could play a more important role in the delivery of peptides and proteins because of their superior permeability characteristics or the fact that the dosage form can be retained at the site of administration for a prolonged period of time to maximise absorption.

Those reading popular fiction may have been led to believe that the problem in delivering peptides had already been solved. To quote from Arthur Hailey's book entitled 'Strong Medicine' (Hailey, 1984) one learns that

"The way in which the drug would be ingested .... was important. We've researched this exhaustively and recommend delivery by nasal spray. This is the modern coming system .... Peptide 7 will be in an inert saline solution mixed with a detergent (that) assures the best absorption rate .... The best non-toxic (detergent) creating no irritation of nasal membranes had been found".

If only it was so easy! While it is true that certain peptides are well taken up via the nasal route (Su, 1986), totally innocuous absorption enhancers have yet to be discovered and the implications of long term therapy on possible damage to the mucosa need to be resolved.
A universal delivery system for peptides and proteins is neither possible nor perhaps desirable, largely because the types of materials being considered for therapeutic application comprise a diverse range of biological response modifiers (Table 1). They have different physical and chemical characteristics (molecular size, stability, conformation etc) as well as different sites and modes of action within the body. For example a delivery system for tumour necrosis factor or an interleukin by necessity, will be rather different from that for insulin or calcitonin. Furthermore, unlike conventional low molecular weight drugs, biological response modifiers are often involved in complex processes where a whole group of regulatory materials can be involved. The "classical" situation of a single pharmacodynamic agent acting independently on one particular receptor type may not necessarily pertain. For example, it is known that materials such as interferon can act to prime or "up-regulate" the action of another material (Aggarwal et al, 1985). Similarly, the action of one agent may lead to a whole process of actions, often in the form of a cascade process. Consequently the resultant biological response may be determined by an alteration in a delicate balance between a number of inter-related regulatory materials. Clearly, in the development of any potential therapeutic agent and its delivery system it will be essential that such aspects of molecular and biochemical pharmacology are elucidated. The complexity of the properties and actions of regulatory peptides and proteins will mean that the successful development of pharmaceutically elegant delivery systems for peptides and proteins will be a multidisciplinary venture, to include input from disciplines such as biochemistry (the action of enzymes), physiology (membrane permeability), immunology (immunogenicity), physical chemistry (molecular characteristics; solubility, stability).

The main emphasis of the present contribution will be to consider the possibilities and problems for peptide and protein delivery and the different options available for rational drug delivery systems. By necessity comment will also be made on the pharmacokinetics of peptide systems, their assay and preformulation studies and the possibilities of immunogenic reactions.

Kinetic profiles

In many cases the simplest form of a delivery system for peptides and proteins will be the hypodermic syringe containing the drug in a buffered aqueous solution. The appropriate dose of agent is then injected intravenously or subcutaneously according to the desired time pattern. This mode of administration, although ideal from the standpoint of clinical pharmacology, is obviously limited in its widespread applicability to the patient population at large. Even for a simple system (and especially for complex systems providing sustained therapy), essential information is necessary. This includes the dose, dose frequency and the site of action of the drug. Generally speaking, natural peptides and proteins acting as agonists are short-lived in their action and are rapidly metabolised. Furthermore, the body provides these agents as pulses rather than continuously to a particular receptor site (Knobil, 1980; Urquhart et al, 1984). From the outset, the ability to mimic such a pattern of delivery using a novel delivery system will present substantial challenges to the pharmaceutical scientist. Moreover, it is often found that the desired pharmacokinetic profile for a regulatory material in man has yet to be determined since animal models, although useful, may not be entirely suitable. An obvious starting point is studies with infusion pump systems in animal models and more recently the implantable osmotic pump (Alzet) has been employed to provide a response without the necessity of tethering the animal (Obie et al, 1979; Knobil, 1980; Lynch et al, 1980; Ewing et al, 1983). This