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Review

Administration strategies for proteins and peptides

D. Ibraheem, A. Elaissari, H. Fessi *

University of Lyon, F-69622, Lyon, France, University Lyon-1, Villeurbanne, CNRS, UMR-5007, LAGEP- CPE, 43 bd 11 Novembre 1918, F-69622 Villeurbanne, France

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ABSTRACT

Proteins are a vital constituent of the body as they perform many of its major physiological and biological processes. Recently, proteins and peptides have attracted much attention as potential treatments for various dangerous and traditionally incurable diseases such as cancer, AIDS, dwarfism and autoimmune disorders. Furthermore, proteins could be used for diagnostics. At present, most therapeutic proteins are administered via parenteral routes that have many drawbacks, for example, they are painful, expensive and may cause toxicity. Finding more effective, easier and safer alternative routes for administering proteins and peptides is the key to therapeutic and commercial success. In this context, much research has been focused on non-invasive routes such as nasal, pulmonary, oral, ocular, and rectal for administering proteins and peptides. Unfortunately, the widespread use of proteins and peptides as drugs is still faced by many obstacles such as low bioavailability, short half-life in the blood stream, in vivo instability and numerous other problems. In order to overcome these hurdled and improve protein/peptide drug efficacy, various strategies have been developed such as permeability enhancement, enzyme inhibition, protein structure modification and protection by encapsulation. This review provides a detailed description of all the previous points in order to highlight the importance and potential of proteins and peptides as drugs.

Contents

* Corresponding author at: University of Lyon, LAGEP- CPE; 43 bd 11 Novembre 1918, F-69622 Villeurbanne, France. Tel.: +33 4 72 43 18 41.
E-mail address: Fessi@lagep.univ-lyon1.fr (H. Fessi).

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1. Introduction

The revolution of biotechnology has led to the creation of various types of therapeutic proteins (Brown, 2005; Xie et al., 2008; Almeida and Souto, 2007; Tan and Danquah, 2012; Stevenson et al., 2012; Ye et al., 2010; Torchilin and Lukyanov, 2003), with the potential to provide treatment for certain dangerous diseases that have long been thought incurable (Brown, 2005). Biotherapy now has the potential to target chronic and malignant diseases such as cancer (Dougan and Dranoff, 2012; Jaffee, 1999; Chen et al., 2013; Rossi et al., 2013a), dwarfism (Matiasevic and Gershberg, 1966), AIDS (Tomasselli and Heinrikson, 2000), autoimmune disorders (Almeida and Souto, 2007), etc. Moreover, proteins can be used to detect and diagnose diseases (Gelfand, 2001; Hj, 1983) in addition to using proteins as vaccines in order to ensure protection from various diseases (Rossi et al., 2013b; Chura-Chambi et al., 2014).

The chemical structure of proteins allows them to perform specific reactions in the body, increasing efficacy and decreasing undesirable side effects (Russell and Clarke, 1999) (Morishita and Peppas, 2006) (Moeller and Jorgensen, 2008). However, employing proteins for therapeutic purposes is confronted by many obstacles such as their short half-life in the bloodstream, making it necessary to repeat administrations (Putney and Burke, 1998; Putney, 1998), their chemical and physical instability (Bilati et al., 2005), their rapid denaturation in the stomach and intestinal environment, and their retention by the impermeable mucosal tissues in the intestine that hinder oral protein administration (Lee, 2002; Pettit and Gombotz, 1998).

Recombinant proteins have been developed and prepared on a large scale, and they play a dominant role in improving protein-based therapy (Overton, 2014). Somatostatin was the first recombinant human protein fabricated by Genentech in 1977 (Itakura et al., 1977), whereas human insulin was the first recombinant protein to be marketed by Genentech (Buckel, 1996). Since then various recombinant proteins have been prepared using different methods. Most therapeutic proteins are prepared either by using mammalian cells (especially Chinese hamster ovary cells CHO), or *Escherichia coli* (Chu and Robinson, 2001; Swartz, 2001; Russell and Clarke, 1999).

Synthesizing recombinant proteins could solve many problems that have hindered wider clinical applications for therapeutic proteins (Morishita and Peppas, 2006), making it possible to prepare proteins of interest in sufficient quantity, and avoiding the presence of human pathogenic viruses (Buckel, 1996; Swiech et al., 2012). However, many drawbacks restrict the use of recombinant proteins *in vivo*, such as their instability and incapacity to reach intracellular targets (Russell and Clarke, 1999).

Various techniques have been developed to improve the physicochemical properties of proteins, protect them in biological media and deliver them to their target (Torchilin and Lukyanov, 2003). In this review we illustrate the techniques that have been used to achieve the objectives described above, such as protein structure modification, the use of special adjutants that can enhance protein absorption, inhibit protein degradation, or using different protein encapsulation techniques.

This review also highlights the potential therapeutic applications of proteins and peptides and the obstacles that limit their widespread clinical use. It presents a description of the most frequently used protein administration routes.

2. Potential uses of proteins in the medical field

The development achieved in the field of biotechnology, in addition to better understanding of diseases and pathogenesis, has opened new horizons for using proteins to prevent and treat of various kinds of dangerous diseases (Drews, 2000; Russell and Clarke, 1999).

At present, medical biotechnology has proved its efficacy in treating and discovering many diseases and disorders, as shown in Fig. 1.

In the following paragraph we highlight some of the therapeutic applications of proteins. Since the advent of monoclonal antibodies in 1975 (Köhler and Milstein, 1950), many diagnostic and therapeutic antibodies have found their way to clinical applications after being approved by the Food and Drug

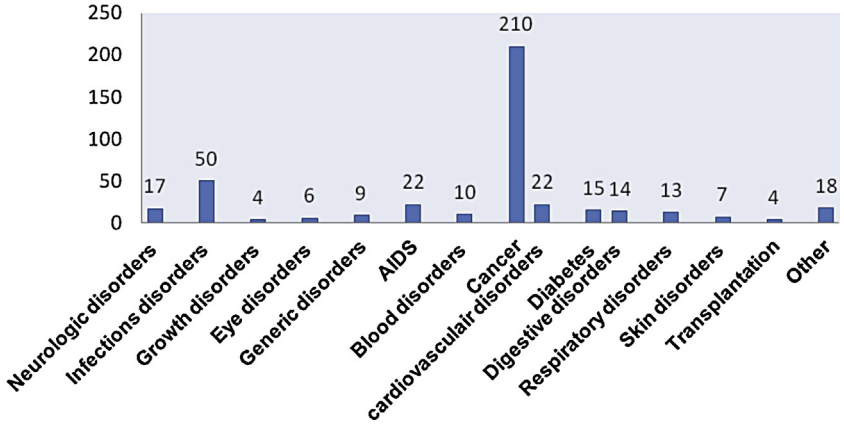

Fig. 1. Medical biotechnology in development by therapeutic category (Almeida and Souto, 2007).