Editorial

Peptides as a Novel Therapeutic Approach for Neurodegenerative Diseases

Peptides and proteins are the natural means of activating and inhibiting cellular mechanisms. Normal functions of the central nervous system (CNS) largely dependent on protein-protein interactions (PPIs) signaling pathways. Affecting receptors and targets of naturally occurring peptides and proteins is a very promising therapeutic strategy for the treatment of neurodegenerative diseases. PPIs can be readily addressed with small molecule drugs. Several small-molecule drugs that do address PPIs are natural products. Since last two decades extensive research is going on to explore other approaches for targeting specific intracellular PPIs. After many years of stagnation, peptide therapeutics once again became the focus of innovative drug development efforts backed up by venture funds and biotechnology companies.

Understanding of the pathophysiological mechanisms underlying neurodegenerative diseases helped unravel novel therapeutic targets, indicating that manipulation of enzymes activities, neurotrophic factors, receptors as well as cellular maintenance and defense mechanisms could mitigate disease progression and alter disease course. The classic pharmaceutical industry focused drug discovery efforts on synthesizing small molecules that would activate, antagonize or imitate activities of protein targets such as receptors or enzymes. Discovery and synthesis of small molecule that could interact and affect the desired therapeutic target without undesired side effects is challenging. Therapeutic peptides are a class of peptide-based drugs capable of eliciting a therapeutic response by modulation of targets within or on the surface of cells. Peptides are advantageous because they are amenable to rational design, have high specificity for their targets and can target almost any protein of interest [1].

Peptide therapeutics has several specific obstacles needing resolution before it could be employed on a big scale. These obstacles include low stability and rapid turnover of the peptides, complicated cellular and CNS penetration, possible immunogenicity, and high manufacture costs and technical complexity. Significant progress has been made in the last few years to overcome disadvantages in peptide design such as short half-life, fast proteolytic cleavage, and low oral bioavailability. Recent technological breakthroughs such as increased *in vivo* stability, new solutions for CNS delivery as well as reduced cost of manufactureled to significant improvements in some of these limitations. Designer peptide drugs overcome the unattractive pharmacological properties of native peptides and protein fragments and frequently feature nonnatural amino acid or backbone replacements, cyclic or multimeric structures, or peptidic or nonpeptidic delivery modules. With their high specificity and low toxicity profile, biologicals offer viable alternatives to small molecule therapeutics. Currently, the field of protein and peptide-based therapies is one of the expanding sectors of the pharmaceutical industry with over 70 marketed peptide therapies and over 150 peptides in clinical development [2].

Peptides have many advantages as therapeutic interventions for neurodegenerative diseases. Peptides have high specificity for their targets and are highly potent. Very low levels of the therapeutic peptides are therefore required to execute the desired effect. Endogenous peptide hormones execute complex modulatory functions in a very specific and well regulated manner in the CNS, and peptide therapeutics can mimic these activities. Contrasting many small molecules, peptides are efficiently metabolized by endogenous enzymes, and do not accumulate in the tissues. This can be a disadvantage causing rapid degradation of the therapeutic peptide, yet it increases the safety profile of these therapeutic tools. Unlike small molecules, peptides have a reduced amount of drug–drug interactions and usually have reduced toxicological complications.

Short *in vivo* half-life, due to endogenous peptidase breakup and rapid renal and hepatic clearance of the peptides therapies, is one of the major obstacles in the development of peptide drugs. Many peptide drugs are cleared from the blood within minutes consequentially leading to unsatisfactory delivery to the target organ. Novel stabilizing strategies employing non natural amino-acids substitutes and peptide structure modifications in order to achieve enzymatic resistance have been effectively used. Peptides' delivery mode posesanother major challenge. Oral administration leads to rapid degradation and is therefore unfeasible. Subcutaneous injection technology has progressed in the past years resulting in reduced discomfort and manufacture costs. New strategies such as transdermal administration and intranasal delivery have also been developed.

Peptide therapies for treating neurodegenerative diseases comprise several unique problems. Peptide delivery into the CNS is complicated by the blood brain barrier (BBB). Since peptides cannot cross cell membranes, specific and selective transporters enable peptides and regulatory proteins to cross the BBB and to enter cells by specific saturable and non-saturable mechanisms [3]. Specific transporters that deliver endogenous peptides through the BBB could be utilized in order to deliver therapeutic peptides into the brain. Several other strategies were developed over the past years to enhance protein/peptide drug delivery over the BBB. These include modification of lipid solubility of these drugs, prodrug delivery bioconversion strategies, and the use of colloidal drug carriers (liposomes, nanoparticles, and nanogels) [4]. Intranasal delivery of proteins to the CNS has been successfully demonstrated in animal models and in human subjects [4].

The safety advantages of peptide therapeutics, the specificity of their mode of action and the breakthroughs achieved in solving several problems in peptides stability, delivery and manufacturing encourage developing novel peptide therapeutics for CNS disorders. Yet, as elaborated above, technical challenges that must be overcome still exist and must be resolved for peptides to become practical therapeutic tools. In this special issue state-of-the-art information and novel approaches in the field of

peptide therapeutics for CNS indications will be discussed. Potential new targets in various neurological diseases will be presented and means to overcome obstacles limiting the use of peptides as the powerful therapeutic tools will be addressed.

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Zakir Khan
Guest Editor
Institut Pasteur, Unité de NeuroImmunologie Virale
Departement de Virologie, CNRS,UMR 3569
F- 75015 Paris
France
E-mail: zakirq.khan@gmail.com