PEPTIDES AND PEPTIDOMIMETICS IN NEUROPHARMACOLOGY (REVIEW)

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ABSTRACT

Peptides and peptidomimetics are a major field of bioorganic chemistry research. We endeavored to describe the current trends in medicinal and bioorganic chemistry regarding the design of drug molecules which are peptide mimetics. To this end, we reviewed the literature regarding peptidomimetics classification, new research data on innovative potential drug molecules, current research, and its perspectives. Potential or current neuropharmacological agents that possess a peptide bond in their molecules and can be used in the treatment of pain or Alzheimer's disease are of particular interest to our study. The inclusion criteria required that the studies explore peptides, peptide mimetics, and peptidomimetics or mimetics of peptides that show biological activity in the central/peripheral nervous system. Electronic search strategies were developed and undertaken, and relevant articles were selected and reviewed. A considerable number of pharmacological agents showing pharmacotherapeutic relevance were identified and reviewed regarding biological activity in the nervous system. The ones more closely reviewed are prospective or proven effective neuropharmacological agents that are analogs of peptides/oligopeptides. The potential for discovery of various peptides and peptidomimetics, which can affect the pathogenesis of pain, neurodegenerative diseases (Alzheimer's disease, Parkinson's disease and others) offers to broaden the scientific horizon; in the end leading to the synthesis of potential alternatives to current pharmacotherapeutics. Translational research can be encouraged after careful consideration of the risk-benefit ratio.

Keywords: peptides, peptidomimetics, neuropharmacology, drug design.

INTRODUCTION

Background: Peptides and peptide mimetics, i.e., peptidomimetics (PM) can be viewed as one fascinating field of discovery for medicinal chemistry and modern drug design, as they constitute a major field of bioorganic chemistry and pharmacology research. In a recent tutorial review Lenci and Trabocchi provide good definitions of PM, explain their new classification versus the old one, as well as point out the advantages of peptidomimetics over peptides [1]. A contemporary mini review of peptides and peptidomimetics in drug design with a focus on neuropharmacology is the goal of our literature survey.

Definitions of peptides and peptidomimetics: Peptides are important natural molecules, composed

of natural amino acids bound together via peptide bonds, they function biologically as antibiotics, toxins, antibodies, enzymes, venoms, neurotransmitters, and hormones. "Methods to modify natural peptides and those discovered de novo by man using directed evolution have generated peptide ligands with improved properties, such as high affinity, excellent target specificity and good plasma stability" as stated by Goldman and Ullman [2].

On the other hand, according to Hruby and Cai, peptide mimetic is a nonpeptide ligand with the structure-activity relationships of a peptide for the same target [3]. Earlier than this definition, Vagner, Qu, and Hruby also define PM as "compounds whose essential elements (pharmacophore) mimic a natural peptide or protein in 3D space and which retain the ability to interact with the biological target and produce the same biological effect. They are designed to circumvent some of the problems associated with a natural peptide: e.g., stability against proteolysis (duration of activity) and poor bioavailability" [4]. In their review in 2008, Vagner, Qu and Hruby envision that peptidomimetic research will continue to be an indispensable tool of structure-activity relationships in drug discovery for the foreseeable future. How right they were in their assumption remains to be proven in our review [4].

Nasim and Qureshi in their chapter about the "Role of structural biology methods in drug discovery" provide a good schematic illustration of the methods involved in drug discovery and development in the field of PM [5].

Contemporary drug discovery mandates the preliminary search for suitable lead compounds for target synthesis by actively using libraries with databases, containing a list of lead compounds. Such a database as a tool in drug discovery is for example ASINEX [6]. An excellent illustration of the fundamental role of medicinal chemistry with peptides and peptidomimetics in the whole long process of discovery and development of drug molecules is provided by Chu and co-authors in their comprehensive and systematic review of the literature on peptide-based ligands and their use in the affinity purification of established and upcoming biological drugs [7].

A team of Italian researchers in 2020 have created an excellent mini review of the bioinformatics tools - computational and biosimulations in peptide design. D'Annessa and co-authors argue that peptides and PM are nowadays strongly re-emerging as candidates in the development of therapeutic strategies against a plethora of diseases in which a major role is played by protein-protein interactions. They highlight the significance of peptides and PM in pharmacological applications, also having a potential strong economic impact on the pharmaceutical industries [8].

With the current review we aim to identify up-to-date trends in medicinal and bioorganic chemistry regarding the design of drug molecules which are peptide mimetics, and act upon the central or peripheral nervous system. We reviewed the literature regarding peptide mimetics classification, new research data on innovative potential drug molecules, current research, and its perspectives in neuropharmacology.

The inclusion criteria required that the studies explored: peptides, peptide mimetics, peptidomimetics (PM) or mimetics of peptides that show biological activity in the central/peripheral nervous system.

Our electronic search strategies were developed and undertaken using Google Scholar, PubMed, Springer, to look for published scientific research, as a result relevant articles were selected and reviewed.

RESULTS AND DISCUSSION

A considerable number of publications focusing upon pharmacological agents with pharmacotherapeutic relevance were identified and reviewed regarding biological activity in the nervous system. The ones more closely reviewed are prospective or proven effective neuropharmacological agents that are analogs of peptides/oligopeptides.

In a review from 2018, Perez points to the beginning of peptidomimetic research in the field of neuropharmacology: this was when morphine pharmacological actions were explained as the discovery of the first endogenous opioid enkephalins was done - in the seventies of the previous century, or almost 50 years ago [9].

We firstly want to clarify the peptidomimetics classifications, then to describe the new compounds investigated for neuropharmacological activity. We also strived to compare the two classifications of peptidomimetics: the old one and the new one to each other.

Classifications of Peptidomimetics

Rajeev Kharb and colleagues, in their review of the therapeutic importance of PM in medicinal chemistry [10], use the classification of Ripka, Bursavich and Rich [11, 12] (Table 1) and describe 4 classes of PM: Type I (pseudopeptides), Type II (functional mimetics), Type III (topographic mimetics), and Type IV – non-peptide mimetics that bind to enzyme forms inaccessible to pseudopeptides (e.g., piperidine antagonists, influenza A vaccines).

Type I PMs (Peptide Mimetics, pseudopeptides) are synthesized by structure-based drug design. These PMs are very similar to the peptide backbone while retaining functional groups that can contact receptor binding sites. Some of their structural units mimic short parts of peptide secondary structure, for example β-turns, and have been used to generate lead substances. Many of the early protease inhibitors were designed from substrate/product mimetics of the transition-state or product-state peptide bond for the enzyme-catalyzed reaction. For example, pyrrolinones have peptide-like side chains that correspond to the most active sites of most peptidases and, additionally, are resistant to normal proteolysis because they replace amide bonds with metabolically stable units per amino acid structural unit of parent peptides.

Type II PMs (functional mimetics) are the product of molecular modeling and high-throughput screening (HTS), etc. These are small non-peptide molecules that bind to a peptide receptor. Morphine is the first well-characterized example of this type of PM. Initially, type II mimetics were thought to be direct structural analogues of the natural peptide, but antagonists of many receptors appear to bind to receptor substructures different from those used by the parent peptide. Therefore, functional mimetics may not mimic the structure of the parent peptide. Despite this uncertainty, the approach has been quite successful and has led to several potential structures of drug leads, for example GPCR antagonists.

Type III PMs (topographic mimetics) are synthesized through structure-based drug design, on new backbones that appear unrelated to the original peptides, but contain the core groups located on a new, non-peptide scaffold and serve as topographic mimetics. Several type III PM protease inhibitors have been characterized by X-ray structural analysis of the inhibitor, a peptide derivative, and heterocyclic non-peptide inhibitor complexes. These examples show that alternative scaffolds may also present side chains and interact with proteins in a manner closely resembling the parent peptide, e.g. non-peptide protease inhibitors.

Type IV PMs or non-peptide mimetics, are synthesized with a special technique of drug design - group replacement assisted binding (GRAB). These structures may share common structural and functional features with type I PM, but they bind to an enzyme form not accessible to type I PMs, e.g., the piperidine renin inhibitors [13].

The functional classification of peptidomimetics on the other hand could be constructed according to their mechanism of action as follows:

- GPCR agonists and antagonists;
- Antagonists which are protease inhibitors (anticoagulants, antivirals, antihypertensives)
- Other enzyme inhibitors;
- Antibody-like PMs, for improved vaccines.

Peptidomimetics in neuropharmacology

A little-known fact about morphine is that this prototype opiate was the first medically well-characterized functional peptidomimetic, as pointed out in Perez review on Designing peptidomimetics [9]. As an opioid receptor agonist, morphine mimics the action of natural opioid peptides in brain - enkephalins and endorphins, while not having a recognizable peptide structure, and we cannot qualify it as a structural analogue of these peptides. Peptidomimetics, as can be seen from Table 1, also include medications that have been used for years in psychiatry: tricyclic, tetracyclic antidepressants, lots of antipsychotics, which are GPCR blockers in the brain. As an example of a promising direction in drug design, PMs which are derivatives of μ-conotoxins (peptides extracted from the venom of a marine snail) and blockers of voltage-sensitive Na^+ channels can be indicated [15].

Examples *of potential neuropharmacological agents*

Examples of PMs that have been studied as potential neuropharmacological agents include:

- Analgesic derivatives, analgesic peptide mimetics - enkephalin mimetic drugs, morphinomimetics, also conopeptidomimetics [16, 17];
- Nootropic and anti-inflammatory PMs - with applicability in Alzheimer's disease, etc. dementias and neurodegenerative diseases - for example, BACE1

Table 1. Types of Peptidomimetics (according to Estuarte and Rich [13] with exemplary representatives of each group).

Peptidomimetics		Design	Examples with the year of the drug prospect
Type I	**Mimetics of the peptide skeleton**	Substrate-based design	**Pseudopeptides, e.g.,** proteasome **inhibitors** [14] with first representative – Bortezomib, 2003;
Type II	**Functional mimetics**	Molecular modeling, HTS	**Antagonists of metabotropic receptors**: tricyclic antidepressants: amitriptyline 1961, antihistamines and antipsychotics chlorpromazine, 1955; clozapine, 2002; tetracyclic antidepressants - mianserin
Type III	**Topographic mimetics**	Structure-based, rational drug design	**Non-peptide protease inhibitors (PI)** - ACE-inhibitors, renin inhibitors: Aliskiren, 2007; antiviral PI: 1. Antiretroviral protease inhibitors– Saquinavir, 1995; 2. Anti- HCV: Telaprevir, 2006; Boceprevir, 2011
Type IV	**Non-peptide PM**	GRAB – Group Related Assisted Binding	**Piperidine inhibitors** - Donepezil (Aricept), 1997

- (aspartyl protease) inhibitors [18, 19], galantamine derivatives acting as ACE (Angiotensin Converting Enzyme) inhibitors, currently being investigated as potential or candidate-drugs [20 - 23]; neurotrophin peptidomimetics [24, 25];

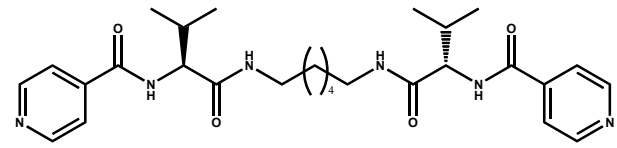
- Anticonvulsants - somatostatin mimetics [26, 27];
- Antiaggreagating peptidomimetics [28] ;
- L-valine peptidomimetics.

The development and implementation in practice of peptidomimetic compounds with a neuroprotective and positive effect on cognitive functions is extremely interesting and promising from a scientific and therapeutic point of view. Development in this direction was provided by Martin Bruno and collaborators with the development of a peptidomimetic ligand of the NGF (neural growth factor) receptor [29]; as well as other authors who incorporate PM in the design of new drugs, including in cases with impaired cognitive functions requiring neuroprotection [30 - 32].

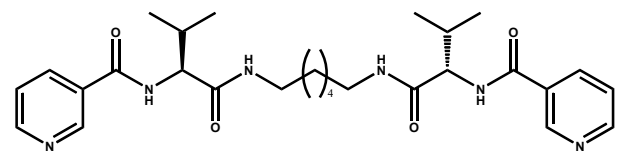
L-valine peptidomimetics as BCAA and Pyridine derivatives

L-valine peptidomimetics belong structurally to the group of non-peptide PMs. They are low molecular organic gelling agents and possess a unique chemical structure based on the essential branched-chain amino acid (BCA) L-Val linked via an amide bond to either nicotinic (m-pyridinic) acid -[M] or isonicotinic (p-pyridinic) acid [P] on one side, and an alkyl spacer with 3 and 6 methylene groups on the other side, also via amide linkages [33, 34]. The substances M-6 and P-6, illustrated below with their chemical formulas and names, were chosen as representatives of a group of 16 newly synthesized derivatives, exhibiting the best biological activities [34]. Both they are positional isomers, containing in their structures moieties of either nicotinic or isonicotinic acids. The potential of such type of derivatives for drug synthesis has yet to be studied in detail [35, 36].

Through QSAR analysis, it was found that these



P-6 - [N, N'-Bis(N-isonicotinoyl-L-valyl)-diamino-hexane



M-6 - [N, N'-Bis(N-nicotinoyl-L-valyl)-diaminohexane]

isomers of L-valine derivatives, which have six methylene groups as a hydrophobic spacer, were the most effective as neuropharmacological agents [37 - 39]. They improved cognitive processes, as this was demonstrated in both group-reared and socially isolated white mice, and the mechanism of action of these substances has yet to be clarified [37, 41].

The studies of L-valine PMs were the subject of a multi-year research on joint scientific projects developed at the Institute of Neurobiology (Bulgarian Academy of Sciences), University of Chemical Technology and Metallurgy - Sofia, Medical University - Sofia, "Jaume I" University, Castellon, Spain, Hebrew University and Hadassah University Hospital - Jerusalem, Israel [34 - 42].

CONCLUSIONS

Given the vast array of potential drug molecules applicable in the field of neuropharmacology, we can conclude that peptides and their analogues in the face of peptide mimetics are a major channel of discovery for medicinal chemistry and pharmacological development. This is a whole new and promising interdisciplinary sector of applied drug chemistry and neuropsychopharmacology. Moreover, the potential for discovery of various peptides and peptidomimetics, which can affect the pathogenesis of pain, Alzheimer's disease, and other socially significant neurological diseases offers to broaden the scientific horizon; in the end leading to the synthesis of potential and, hopefully, safer alternatives to current pharmacotherapeutics.

Translational research can be encouraged after careful consideration of the risk-benefit ratio.

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