

Editorial

Use of peptides combine with nanotechnology and molecular imaging – new tools for diagnosis and treatment of neuropsychiatric disorders

Utilização de peptídeos combinados com nanotecnologia e imagem molecular – novos métodos para diagnóstico e tratamento de doenças neuropsiquiátricas

Many peptides and short proteins have been used as drugs since the commercial introduction in the 1920s and 30s of insulin, thyroid hormone and factor VIII. Despite the fact that peptides have been used for a century to diagnose and treat several kinds of diseases such as diabetes and hypothyroidism, they are now considered the new generation of biologically active tools. Peptides are key regulators in cellular and intercellular responses, with an enormous potential for the diagnosis and treatment of various pathological conditions such as neuropsychiatric disorders.¹

Several lines of evidence indicate that peptides and proteins exert multiple biological actions in the brain such as neurotransmission and neuromodulation, regulation of the cerebral blood flow, regulation of cerebrospinal fluid secretion, modulation of the blood brain barrier (BBB) permeability to nutrients and regulation of the internal environment of the brain.² Neurotransmitter and hormone peptides are associated to the modulation of behavior, stress, anxiety, aggressiveness, thermoregulation, sleep, pain, learning, memory, drug abuse, alcohol intake, and anorexia. Peptides have become important targets in neuropharmaceutical drug design for the diagnosis and treatment of a wide variety of central nervous system (CNS) disorders.¹

In spite of their clinical potential, native peptides presented limited use due to their poor bioavailability and low stability in physiological conditions. Peptides that act in the CNS have been significantly impeded by the difficulty of delivering them across the blood brain barrier. The ability of a peptide to cross the BBB and enter the brain depends on several compositional factors, including size, flexibility, conformation, biochemical properties and arrangement of amino acids. These factors determine the lipophilicity, hydrogen bonding potential, and molecular weight of the peptide. With greater understanding of the biology of the BBB, peptide and protein drug sites of action, and advances in design principles in medicinal chemistry used to change physico-chemical and/or biological properties of peptides and proteins, it will be possible to design and optimize potential peptide drugs with improved potency, selectivity and therapeutic efficacy.

The brain as a major control center is an important target for many of these neuropharmaceutical drugs and rational drug design is now being used to improve brain bioavailability so that potential therapeutics can exert their desired pharmacological effects. Considerable efforts have been made to design new drugs based on peptides, recent developments in technology and science have provided the tools and opportunities to expand the range of peptide based drugs in an effort to further understand and diagnose neuropsychiatric disorders.³

Two technologies have been used to improve and add diagnostic value to CNS peptide development: *nanotechnology* and *molecular imaging*. Nanotechnology has produced nanoparticles (NPs) with important applications in biological sciences. NPs are solid colloidal particles, made of polymeric materials ranging in size between 1 and 100nm. When metallic NPs are magnetic, they

can be manipulated by an external magnetic field gradient. This action at a distance, combined with the intrinsic penetrability of magnetic fields into human tissue, opens up many applications involving the transport and/or immobilization of magnetic NPs, or of magnetically tagged biological targets. Thus, NPs can be used to deliver a cargo to a targeted region of the body. Nanoparticles have been used for a broad array of applications, and the most promising one is the transport of drugs across the BBB. Nanoparticles are highly advantageous as delivery vehicles: the loading and release of cargo can be controlled; specific molecular-targeting factors can be attached; a hydrophilic coating can prevent undesired uptake of the nanoparticle by the reticulo endothelial system; and the matrix nature of the nanoparticle can provide protection against enzymatic and/or chemical degradation of the active agent. Some examples of peptides which have been transported to the CNS by nanoparticles are Z-DEVD-FMK, a specific caspase inhibitor, and NC-1900, a vasopressin fragment analogue.

Molecular imaging is used to study physiological, biochemical and pharmacological processes with nanomolar sensitivity in vivo. The imaging techniques, positron emission tomography (PET) and single photon emission computerized tomography (SPECT) employ biomarkers labeled with positron- or γ -emitting radioisotopes, enabling the localization of the specific molecule in the target tissue. PET and SPECT have clinical applications in neurological diseases such as Parkinson's and Alzheimer's diseases, and several research applications in most neuropsychiatric disorders.⁴

Binding affinities in low nanomolar range are a prerequisite for successful peptide tracers. Some peptide radioligands include those used for somatostatin receptor targeting; Bombesin a ^{99m}Tc-ligands

with high affinity for GRP receptor; and Substance P radioligands with affinity for the NK1 receptor, overexpressed in human glioblastoma.⁵

In Alzheimer's disease (AD) an amyloid imaging brain scan could be developed with $A\beta^{1-40/42}$ peptide radiopharmaceuticals because radiolabeled forms of these molecules are promptly deposited at preexisting amyloid plaques in tissues sections of autopsy AD brain. Several groups in the world are working in these potential peptide radiopharmaceuticals that could be used for imaging brain amyloid in living subjects with AD. This neuropeptide are likely to be made transportable through the BBB, and provide a diagnostic test specific for AD and for assessing the effects in brain of drugs that inhibit the formation of $A\beta$ amyloid.⁴

In summary, the combined use of radiolabeled and nanoparticles encapsulated peptides offers tremendous hope in further understanding and diagnosing brain disorders by crossing the BBB and providing highly sensitive molecular images. However, they must be further studied for their potential diagnosis and clinical applications.

Luciana Malavolta, Francisco Romero Cabral, Lionel Fernel
Gamarra Conterras, Anna Maria Ringheim
Instituto Israelita de Ensino e Pesquisa Albert Einstein,
São Paulo (SP), Brazil

Rodrigo Affonseca Bressan
Instituto Israelita de Ensino e Pesquisa Albert Einstein,
São Paulo (SP), Brazil
Laboratório Interdisciplinar de Neurociências Clínicas (LiNC),
Universidade Federal de São Paulo (UNIFESP),
São Paulo (SP), Brazil

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Writing group member	Employment	Research grant ¹	Other research grant or medical continuous education ²	Speaker's honoraria	Ownership interest	Consultant/ advisory board	Other ³
Luciana Malavolta	IIEPAE	IIEPAE Instituto UNIEMP	-	-	-	-	-
Francisco Romero Cabral	IIEPAE	IIEPAE	-	-	-	-	-
Lionel Fernel Gamarra Conterras	IIEPAE	IIEPAE CNPq	-	-	-	-	-
Anna Maria Ringheim	IIEPAE	IIEPAE	-	-	-	-	-
Rodrigo Affonseca Bressan	IIEPAE*** UNIFESP**	CNPq*** FAPESP*** IIEPAE***	Novartis*** Eli-Lilly*** Janssen-Cilag*** AstraZeneca***	Novartis* Eli-Lilly* Janssen-Cilag* AstraZeneca*	-	Astra-Zeneca* Janssen-Cilag*	AstraZeneca* Eli-Lilly* Janssen-Cilag*

* Modest

** Significant

*** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.

Note: IIEPAE = Instituto Israelita de Ensino e Pesquisa Albert Einstein; UNIFESP = Universidade Federal de São Paulo; FAPESP = Fundação de Amparo a Pesquisa de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico.

For more information, see Instructions for authors.

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