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Development of the scientific and methodical approach to searching for and developing new peptide inhibitors of GPIIb/IIIa receptors of thrombocytes

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Abstract

Inhibitors of GPIIb/IIIa receptors of thrombocytes are used in clinical practice for inhibiting the aggregation function of thrombocytes. Widening their range due to the use of peptide compounds seems relevant. This research is devoted to development of a scientific and methodical approach to searching for and developing new peptide inhibitors of GPIIb/IIIa receptors of thrombocytes. With the help of the information and analytical methods, the modern approaches to searching for and creating peptide inhibitors of GPIIb/IIIa receptors of thrombocytes have been assessed. System analysis in their nomenclature was used. In the process of finding and creating new inhibitors of GPIIb/IIIa receptors of thrombocytes, peptide compounds are used with the structure similar to the RGD amino acid sequence in various modifications. The main types of modifications have been systematized. Computer simulation allows optimizing the search and selection of the most promising "candidates" at early stages. The formed scientific and methodical approach to searching for and development of new peptide compounds with antiaggregatory activity involves computer modeling of "hybrid" molecules containing several pharmacophore fragments in a single molecular system. An important aspect of creating new peptide inhibitors of GPIIb/IIIa receptors of thrombocytes is developing efficient methods for their stabilization and improving bioavailability.

Keywords: inhibitors of GPIIb/IIIa receptors of thrombocytes, peptide compounds, RGD amino acid sequence, computer modeling; hybrid molecules, pharmacophore models, medications.

INTRODUCTION

Inhibitors of GPIIb/IIIa receptors of thrombocytes (inhibitors of GPIIb/IIIa) are prescribed in clinical practice for inhibiting the aggregation function of thrombocytes in case of disruptions of coronary circulation accompanied by pathological thrombosis. The range of inhibitors of GPIIb/IIIa is very limited, and includes such medications as Abciximab (ReoPro), Ruciromab (Monafram), Eptifibatidum (Integrilin), Tirofiban (Aggrastat) [1, 2].

The scientific and methodical approach to expanding the range of inhibitors GPIIb/IIIa involves the use of peptide compounds due to their physical, chemical and conformational diversity, low toxicity and good immunogenicity, good affinity to peptide integrin receptors [3-6].

This research is aimed at developing scientific and methodical approach to searching for and developing new peptide inhibitors of GPIIb/IIIa with antiaggregatory activity.

MATERIALS AND METHODS

The modern approaches to searching for and developing new peptide inhibitors of GPIIb/IIIa were assessed by means of informational and analytical methods. The system analysis of the nomenclature of peptide inhibitors of GPIIb/IIIa was applied.

RESULTS

The nomenclature of GPIIb/IIIa inhibitors of peptide or peptide-like structure is represented in the clinical practice by medications Eptifibatidum and Tirofiban intended for treating acute coronary syndrome and for introduction in case of percutaneous coronary interventions. These medications can inhibit thrombocytes' aggregation by over 90%; their prescription recommendations correspond to class IIa with the level of evidence equal to C [7].

Eptifibatidum (Integrilin, "Cor Theraupetics/Schering Plough") is a low-molecular synthetic cyclic heptapeptide that contains 6 amino acids and mercaptopropionyl residue, desaminocysteinyl. Heptapeptide contains a KGD (lysine-glycine-asparaginic acid) amino acid sequence, similar in the structure to RGD (arginine-glycine-asparaginic acid), but with arginine replaced by the positively charged lysine. The cyclic structure of heptapeptide helps its stabilization, and reduces the probability of proteolytic degradation. Eptifibatide is administered bolus intravenously (once or twice) followed by long supporting 24-48-hour infusion. Eptifibatide almost completely inhibits thrombocytes' aggregation immediately after bolus administration, and supports the level of blocking GPIIb/IIIa receptors of thrombocytes throughout the entire period of administration. Aggregatory activity of thrombocytes is restored within 4-6 hours after the end of Eptifibatide infusion. The cyclic heptapeptide has high specificity toward GP IIb/IIIa receptors of thrombocytes, and does not have any significant effect on the activity of other intergin receptors [1, 2, 7, 8].

Tirofiban (Aggrastat, "Merck"). Chemical name - N-(butylsulfonyl)-4-[4-(piperidyl) butoxy]-L-phenylalanine (in the form of hydrochloride). Tirofiban is a molecular compound that is a non-peptide tyrosine derivative, or peptide mimetic. A peptide mimetic imitates the spatial structure of an RGD amino acid sequence; however, it does not contain peptide bonds, so the compound is resistant to the effect of proteases. Tirofiban is introduced bolus intravenously, followed by supporting infusion up to several days long. Infusion administration is made first for 30 min with high load dose, followed by longer infusion (up to several days) with lower supporting dosage. Several minutes after the introduction, platelet aggregation is almost completely inhibited. The aggregative activity is restored within 8 hours after the end of infusion [1, 2, 7, 8].

Searching for inhibitors of GPIIb/IIIa among peptide compounds has become possible due to significant advances in the area of the technology of peptides' biological and chemical screening. The peptide compounds mediate a number of physiological and pathological processes in the human body due to their good affinity with intergin receptors, easily metabolizing in the organism into non-toxic inactive derivatives. Physical, chemical and conformational diversity of the peptides allows them to be used as priority candidates in the search and creation of new inhibitors of GPIIb/IIIa with antiaggregatory activity [3, 4, 5].

GPIIb/IIIa receptors of thrombocytes function due to their ability to identify two characteristic amino acid sequences. The first sequence Arg-Gly-Asp (RGD) is contained in the structure of vitronectin, fibronectin, fibrinogen and von Willebrand factor. The second sequence Lys-Gln-Ala-Gly-Asp-Val (KQAGDV) is located on the carboxyl end of fibrinogen γ-

chain [9]. That is why peptide compounds containing RGD and KQAGDV chains of amino acids are actively studied as promising "candidates" for creating new inhibitors of thrombocytes' aggregation [10-13].

When designing new peptide inhibitors of GPIIb/IIIa, various modifications of the RGD sequences are most commonly used. Examples of these modifications are shown in Table 1.

Most frequently, the following modification of RGD sequences are used: basic five- and seven-membered peptides; creating a cyclic structure; presence of arginine or proline at the N-end in the structure; presence of the Gly—Gly gap and/or aspartic acid residue in the structure; replacement of arginine with lysine or with amidine- or benzamidine- containing groups.

One of efficient methods of optimizing the process of searching for new peptide inhibitors of GPIIb/IIIa and minimizing the risk of failures is computer simulation, which consists in using computational methods to choosing the most promising "candidates" at early stages. The method allows to predict physico-chemical properties, biological activity, metabolism, toxicity of organic compounds with sufficient accuracy [18, 19].

The main approaches in computer simulation of organic compounds are focused on the structure of ligands or on the target. In the first case, a learning sample with the information about the structure and biological activity of the previously studied compounds is used. Predictive modeling of new compounds is performed in built quantitative (QSAR) and classification (SAR) structure-activity relationship models [18, 20].

When focusing on the target, the interaction of the studied organic compounds with the macromolecule target is analyzed. Using the methods of NMR, x-ray crystal analysis, molecular modeling, information is obtained about the spatial (3D) structure of the target, potential ligand molecules are docked to the binding center, the values of the assessment function of the binding energy (scoring function) are calculated, and promising compounds for experimental studies are selected. An important issue in such studies is improving the function of assessing the energy of ligand interaction with protein [21, 22]. Virtual screening with the use of computer technology allows choosing ligands for the specified target, including the use of publicly available databases of chemical compound models [20].

An example of successful computer modeling of new peptide inhibitors of GPIIb/IIIa involved assessment of GP IIb/IIIa thrombocytes' receptor interaction with peptides of type "A-b-C-Asp-D" where A, B, C, D are L-amino acid residues; Asp is the residue of L-aspartic acid; and C is glycine or alanine. As a result, 20,000 peptides with antiaggregatory properties were modeled [23, 24].

Computer modeling of biologically active peptides is a promising area, as confirmed by the results of numerous studies [10, 15-17, 24, 25]. Experimental computer modeling of peptide inhibitors of GPIIb/IIIa unites the use of similar methods. The multistage research involved computer modeling methods based on calculations of binding substances with GP IIb/IIIa receptors on thrombocytes, automated peptide synthesis, flash- and reversed phase chromatography, NMR spectroscopy ^{1}H, mass spectrometry, IR spectroscopy, elemental analysis and Born's turbidity method [10, 15-17, 24, 25]. Examples of peptide compounds - inhibitors of IIb/IIIa GP with high antiaggregatory activity are shown in Table 2.

Table 1. Types of modifications of the RGD sequence in peptide inhibitors of GP IIb/IIIa

Type of modification	The purpose of modification	Source
Preferred sequence: P-X_1-X_2-X_3-D-X_4, where X is an amino acid; X_1 and X_3 are small ones like glycine; X_2 is largeone like isoleucine or cyclic type of proline; X_4 is an amino acid with aromatic lateral chain.	Intensification of the antiaggregatory activity	[14]
Cyclic structure	RGD-containing linear peptides are inactive and unstable due to the rapid enzymatic degradation in blood plasma. Cyclic peptides have rigid three-dimensional structure, and are therefore more stable	[5]
Five- and seven-membered peptides with Arg-Gly-Asp-Ser or Arg-Gly-Asp-Phe amino acid sequences	The number and sequence of amino acid residues determine the peptide's affinity to the integrin receptor. These sequences most effectively inhibit thrombogenesis	[5]
Presence of arginine at the N-end	For intensifying the antiaggregatory activity	[15]
Replacement of arginine with lysine	For intensifying the aggregatory activity. Lysine improves peptides' specificity to the GPIIb/IIIa-receptor complex	[10,15,16]
Replacement of arginine with amidine- or benzamidine- containing groups	With the purpose of improving peptides' stability to enzymatic decomposition	[10,15,16]
Presence of proline at the N-end	Proline improves peptides' specificity to the GPIIb/IIIa-receptor complex	[14].
Aspartic acid residue	For intensifying the antiaggregatory properties. It mediates peptide's ability to form an ion bond with an ion of magnesium at the active site	[14, 17].
Presence of the Gly—Gly gap	Ensures tension of the peptide bond with formation of more rigid conformation, and has positive effect on the antiaggregatory activity	[15]

Table 2. Peptide inhibitors of GP IIb/IIIa with high antiaggregatory activity

Inhibitor of GP IIb/IIIa	Source
ARGDS-NH_2	Vasilyeva T. M. et al. (2006) [5]
RGD-dFK	Vasilyeva T. M. et al. (2006) [5]
Arg-Gly-Gly-Asp-Trp	Belushkina, N. N. et al (2011); Lotorev D. S. et al. (2012) [10, 15]
Phe-IIa-Ala-Asp-Thr	Alekseev A. A. et al (2012) [17]
His-IIe-Gly-Asp-Asp	Alekseev A. A. et al (2013) [26]
Lys-His-Ala-Asp-Asp	Alekseev A. A. (2015) [24]

DISCUSSION

The range of peptide inhibitors of GP IIb/IIIa is quite limited; currently only two antiplatelet medications of the group of GP IIb/IIIa inhibitors are used in clinical practice, which have peptide (Eptifibatide) or peptide-like (Tirofiban) structure, which is similar to the RGD sequence. Eptifibatide and Tirofiban have different competitive (with fibrinogen and other adhesive peptides) mechanisms of inhibition, and their binding to GP IIb/IIIa receptors of thrombocytes is characterized by relatively low affinity and high dissociation rate of the formed complex. It is necessary to maintain high concentrations of GP IIb/IIIa inhibitors in the blood for efficient blocking activity of GP IIb/IIIa receptors on the surface of circulating thrombocytes. The ability of thrombocytes to aggregate is restored within a few hours after the end of infusion [2, 7, 8].

For creating new peptide GP IIb/IIIa inhibitors, compounds that have a structure similar to the key RGD amino acid sequence in various modifications are used most frequently [5, 9, 10].

The modern approach to searching new peptide GP IIb/IIIa inhibitors involved computer modeling with the use of reliable computational methods of molecular modeling, identification and peptides' optimization. Computer design allows to shorten the period of choosing promising "candidates" for creating new inhibitors of thrombocyte aggregation [18, 19]. In computer modeling of new GP IIb/IIIa inhibitors, the use of compounds of peptide nature is significantly promising [15-17, 24-25].

The strategy for the rational design of inhibitors of GPIIa/IIIa receptors from peptide to peptide mimetic is shown on the example of modeling peptide AmBz-beta-Ala-Asp-Tyr-OH [16]. Scognamiglio et al. (2013) showed a panoramic overview of the general principles of converting peptides into small organic molecules, and highlighted the most interesting results of research in the field of computer modeling of new peptide compounds [23]. The process of peptide transformation into a small molecule includes peptide reconstruction to the minimal active sequence. Then the influence of specific amino acids on the biological activity of compounds is determined by sequential substitution of each residue in the peptide with it. After the assessment of each peptide sequence on the model of the "structure-activity" relationship (SAR), the conformational flexibility of the composition is reduced by introducing restrictions in various positions. Thus, the pharmacophore models are developed, in which functional groups are predetermined, which is crucial for ensuring certain biological activity of the compound [4, 23].

Due to the rational design and the high-performance screening of numerous compounds, peptides play a key role in quick identification of ligands; however, they often feature low bioavailability and low metabolic stability [23]. Therefore, the development of efficient methods of stabilizing peptide compounds is an urgent problem in the process of creating new peptide GPIIa/IIIa inhibitors. One of the directions of solving this task is purposeful modification, such as creating peptide compounds with cyclic structure. Cyclic peptides are more resistant to proteolytic degradation in blood plasma due to their rigid three-dimensional structure [5]. The methods of improving bioavailability of peptide GPIIa/IIIa inhibitors are aimed at improving cell permeability of peptides through the use of new delivery technologies in particular [4].

One of the leading trends of searching for and creating new efficient peptide GPIIb/IIIa-receptor inhibitors is related to designing hybrid molecules with introducing several pharmacophore fragments into the same molecular system. When designing a "hybrid" molecule with antiaggregatory activity, it seems promising to use peptide pharmacophores that contain various fragments that mimic amino acid residues important for binding with GP IIb/IIIa receptors of thrombocytes. In addition, "hybrid" molecules may include at once several pharmacophores that act simultaneously on various ways of thrombocytes' aggregation. Examples of such "hybrid" molecules are modeled compounds, which are heteromerous peptides with a furoxan fragment including two pharmacophores: a peptide inhibitor of GP IIb/IIIa receptors of thrombocytes and exogenous donor of nitric oxide of the furoxan row. The presence in chemical compound of the two pharmacophore groups determines the combined mechanism of its antiaggregatory activity. Peptide grouping of the compound is bound with GPIIb/IIIa receptors of thrombocytes, which results in blocking the interaction of fibrinogen and other adhesion factors according to certain type of receptors and inhibition of the aggregation. A pharmacophore with furoxan cycles acts as a thiol-dependent generator of nitric oxide; as a result of releasing nitric oxide, inhibition of thrombocytes' aggregation occurs [24, 25].

CONCLUSION

The key Arg-Gly-Asp amino acid sequence is contained in the structure of vitronectin, fibronectin, fibrinogen, and von Willebrand factor, and plays an important role in the interaction among GPIIb/IIIa receptors of thrombocytes. In clinical practice, antiaggregatory medications of the group of GP IIb/IIIa inhibitors are used, which have peptide (Eptifibatide) or peptide-like (Tirofiban) structure, which is similar to the RGD sequence.

For creating new peptide GP IIb/IIIa inhibitors, compounds that have a structure similar to the key RGD amino acid sequence in various modifications are used most frequently. The modern approaches to searching for and development of new peptide GP IIb/IIIa inhibitors include the use of advanced methods such as computer modeling of "hybrid" molecules with several pharmacophore fragments included into the same molecular system. In computer modeling of compounds with antiaggregatory activity, peptide pharmacophores that contain various fragments that mimic amino acid residues important for binding with GP IIb/IIIa receptors of thrombocytes may be used.

In the process of creating new peptide GPIIa/IIIa inhibitors, an important area is the development of efficient methods of stabilizing peptide compounds and improving their bioavailability.

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