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Review

The application of sulfur-containing peptides in drug discovery

Jiaoyan Zhao[a], Xuefeng Jiang[a,b,*]

[a] Shanghai Key Laboratory of Green Chemistry and Chemical Process, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China
[b] State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

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ABSTRACT

In recent decades, peptides as potential drugs were more and more explored with the development of non-oral medicine. There into, sulfur-containing peptide is one of the most popular aspects in peptide drugs due to the introduction of sulfur atoms leading unique properties. The purpose of the present review is to focus on the discovery of various sulfur-containing peptides with particular emphasis on their pharmacological mechanisms. This review is organized according to the structures of the sulfur-containing peptides.

1. Introduction

Peptides are composed of amino acids and linked through the peptide bonds. So far, thousands of peptides are found in living organisms and they play a vital role in organisms, such as participate and regulate the functional activities of organism. There are three sources of therapeutic peptides: 1) recombinational peptides, 2) chemosynthetic peptides, 3) natural or bioactive peptides which are produced by human, animals or plants [1,2].

Peptides were deemed to be not the excellent drug candidates during the early years owing to their lower oral bioavailability and easily metabolized features [3]. In recent twenty years, peptides as potential drugs were more and more widely explored with the development of non-oral medicine. The development of new strategies for promoting peptide drugs' productivity and diminishing metabolism is necessary in order to explore more excellent peptide drugs in the market. In comparison with traditional small-molecule drugs, peptide drugs have definite functional mechanisms, improved bioactivities, high specificities and lower immunogenicities. An increasing number of peptide drugs have emerged and they are used for the treatment for various diseases including cancer, hepatitis, diabetes, AIDS and so on [4]. Thereinto, sulfur-containing peptide is one of the most popular aspects due to the introduction of sulfur atom exhibiting unique properties in the peptide drugs [5,6]. For instance, [Met5]-enkephalin was cyclized by two side chains through disulfide-bridge to gain the analogue H-Tyr-c[D-Pen-Gly-Phe-D-Pen]-OH (c[D-Pen2,D-Pen5]-enkephalin; DPDPE). A huge conformational constraint was imposed *via* the 14-membered ring associating with the geminal dimethyl group to make DPDPE be a more selective and potent δ-opioid receptor ligand, and it shows powerful analgesic activities, stability against proteolytic enzymes and improved permeability through the blood-brain barrier [7–10]. Contrasts with native linear angiotensin-(1–7), thioether angiotensin-(1–7) have the capacity against degradation by angiotensin-converting enzyme (ACE). The receptor interaction can be regulated by the introduction of thioether-bridges. D-Ala7, an analogue of angiotensin-(1–7), (along with D-Pro7) can serve as antagonists which cause the disappearance of agonist activity through the modification of position 7. Amazingly, even more effective angiotensin-(1–7) agonist can be given by the introduction of thioether-bridge at position 4 and 7 [11,12]. Sulfur-containing peptides attract much attention in the peptide chemistry community especially in the pharmacy owing to their extraordinary stability and pharmacokinetic profiles [13].

2. Peptide drugs with disulfide

The disulfide bond, one of the most momentous covalent bond exists in peptides, plays multifold roles in peptide drugs. It contributes not only to form S—S bond *via* the oxidation and lead the unique spatial structure, but also to improve peptides' pharmacological activities. The cyclization of peptide through the formation of disulfide bond can stabilize its secondary structure, promote its activity, selectivity, and stability against

* Corresponding author at: Shanghai Key Laboratory of Green Chemistry and Chemical Process, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China.
E-mail address: xfjiang@chem.ecnu.edu.cn (X. Jiang).

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proteases. In addition, the cell permeability of peptide can also be improved by the disulfide bond which is used as reversible covalent linker [13].

The disulfide bond is the most common motif in sulfur-containing peptide drugs. Since the 1980 s, multiple peptide drugs with disulfide bonds have been advanced into clinical therapy successively (Table 1).

Romidepsin (Istodax, Fig. 1) which is a disulfide-bridge cyclized peptide was isolated from *Chromobacterium violaceum* [13]. It was approved by FDA in 2009 for the treatment of cutaneous T-cell lymphoma since it is a potent histone deacetylase inhibitor (HDI). As a prodrug, it has a stable hydrophobic structure where the disulfide bond can be reduced to two free sulfhydryl groups by glutathione in cell and they can combine with zinc ion to block histone deacetylase (HDAC) inhibitor's activity [13,14]. Romidepsin can catalyze deacetylation of lysine residues in histone or non-histone, consequently regulate the expression of genes, exert effect on cell cycle arrest, differentiation and induce apoptosis [15]. The research *in vitro* found its inhibitory activity to the transplanted tumor cells including lung cancer, stomach cancer, and breast cancer. It could enhance the inhibition of Erlotinib to non-small cell lung cancer and also be good for the treatment of leukemia [16].

Oxytocin as a disulfide-bridged cyclic nonapeptide is a hypothalamic neuropeptide hormone (Fig. 1) [13]. It was discovered by Dale in 1906. Because of the peculiar structure of oxytocin neurons, oxytocin has the double action of hormone and neurotransmitter. The related research indicated that its primary role is to promote uterine smooth muscle contraction, so that it was clinically used to induce childbirth and lactation [17,18]. The studies on oxytocin analogues indicated that the disulfide is not the essential group but the size of 20-membered ring has momentous influence on its activities which cannot be maintained by enlarging or shrinking the size of the ring [19].

Atosiban (Tractocile, Fig. 1) [20], a disulfide-bridge cyclized nonapeptide, is developed as a tocolytics by Ferring GmbH for women in preterm labor even for those having a high blood pressure and diabetes. As a representative drug of oxytocin receptor antagonist, it can not only inhibit the oxytocin-mediated release of inositol trisphosphate from the myometrial cell membrane, but also reduce the release of calcium ion stored in myometrial cells by combining with the oxytocin receptor of the myometrium cells and the decidua. As a result, it has a significant effect on relaxing the myometrium, inhibiting uterine contraction, and suppressing the oxytocin-mediated release of prostagianndins F (PGF) and prostagianndins E (PGE) from the decidua [20,21].

Octreotide (Sandostatin, Fig. 1) [13], as a somatostatin analog, is a disulfide-bridge cyclized octapeptide. Compared to natural somatostatin, it shows not only a better activity in inhibiting the release of growth hormone, glucagon and insulin, but also a longer half-life [13,22]. Octreotide inhibits somatotropin, gastro-intestinal and pancreatic hormones by binding to the somatostatin receptors of the tumor cells or other tissue cells with high affinity and specificity. It can also achieve the hemostasis without influencing systemic hemodynamics by decreasing splanchnic blood flow and the pressure of portal veins, since it can selectively lower the pressure of portal veins, reduce the blood flow of esophageal varices and show the effect of liver hemodynamics. Thereby, it has a better therapeutic effect on the patients with cirrhosis along with hemorrhage of digestive tract [23].

Vasopressin (Pitressin, Fig. 2) [24], produced by the nucleus of the hypothalamus, is a cyclic nonapeptide consisting of a disulfide bond. It is used to treat for diabetes insipidus and esophageal variceal bleeding in the clinic owing to its contribution to the reabsorption of solute-free water and the regulation of isotonic concentration of body fluid [24–26].

Desmopressin (DDAVP, Fig. 2) as an analogue of vasopressin has a better metabolic stability and preferable antidiuretic effects on account of its deaminated cysteine at position 1 and the replacement of L-arginine with D-arginine at position 8 [13]. The prolonged antidiuretic effect makes it not only be appropriate for more enuretic disorders including primary nocturnal enuresis, nocturia and central diabetes insipidus, but also avoid other concomitant pharmacological effects [27–31].

As another analogue of vasopressin, terlipressin (Glypressin, Fig. 2) is a prodrug developed by EMA in 1990 as a potent vasoconstrictor [33]. Currently, it is used for hepatorenal syndrome type 1 in certain countries including several in Europe, but it is still in the progress in Canada and USA [32]. The activity of constricting

Table 1
Peptide drugs with disulfide.

Entry	INN (Trade Name)	Therapeutic target	Primary use	Approval
1	Romidepsin (Istodax)	Histone deacetylase	Cutaneous T-cell lymphoma	2009 (FDA)
2	Oxytocin	Oxytocin receptor	Obstetrics	1961 (EMA), 1980 (FDA)
3	Vasopressin (Pitressin)	Vasopressin receptor	Insipidus	–
4	Desmopressin (DDAVP)	Vasopressin receptor	Diabetes insipidus	1978 (FDA)
5	Terlipressin (Glypressin)	Vasopressin receptor	Esophageal varices	1990 (EMA)
6	Nesiritide (Natrecor)	Natriuretic peptide receptor	Cardiovascular	2001 (FDA)
7	Atosiban (Tractocile)	Oxytocin receptor	Obstetrics	2000 (EMA)
8	Octreotide (Sandostatin)	Somatostatin receptor	Acromegly	1998 (FDA)
9	Lanreotide (Somatuline)	Somatostatin receptor	Endocrinology	2007 (FDA)
10	Salmon Calcitonin (Miacalcic)	Calcitonin receptor	Osteoporosis	1977 (EMA), 1995 (FDA)
11	Linaclotide (Linzess/Constella)	Guanylate cyclase receptor	Gastrointestinal	2012 (EMA), 2012 (FDA)
12	Ziconotide (Prialt)	N-type calcium channel	Central nervous system	2004 (FDA)
13	Albiglutide (Tanzeum)	Glucagon-like peptide-1 receptor	Diabetes	2014 (FDA)
14	Dulaglutide (Trulicity)	Glucagon-like peptide-1 receptor	Metabolic	2014 (FDA)
15	Etelcalcetide (Parsabiv)	Calcium-sensing receptor	Secondary hyperparathyroidism	2016 (EMA), 2017 (FDA)
16	Setmelanotide	Melanocortin 4 receptor	Obesity and diabetes	–
17	Pramlintide (Symlin)	Amylin receptor	Metabolic	2005 (FDA)
18	Eptifibatide (Integrilin)	Integrin receptor	Cardiovascular	1998 (FDA)
19	Edotreotide (SomaKit TOC)	Somatostatin receptors	Diagnostic agent	2016 (EMA)
20	Carperitide	Atrial natriuretic polypeptide receptor	Heart failure	1995 (Japan)
21	Parathyroid hormone (Natpara)	Parathyroid hormone	Hypocalcemia	2015 (FDA)
22	Insulin glargine (Toujeo)	Insulin receptor	Diabetes	2015 (FDA)
23	Insulin degludec (Tresiba)	Insulin receptor	Diabetes	2015 (FDA)
24	Lutetium(177 Lu) oxodotreotide (Lutathera)	Somatostatin receptor 2	Neuroendocrine tumor	2017 (EMA), 2018 (FDA)
25	Galliumdotatate Ga-68 (Netspot)	Somatostatin receptor 2	Diagnostic agent	2016 (FDA)

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