



The Importance of Amino Acid and Peptide Chemistry in the Treatment of the Major Diseases: Neuropeptides

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Abstract

During this review, from the reality of the previously published articles, we explained how the peptide bond is formed. This review was divided and different peptide groups were distinguished according to the mode of action of the various peptides, whether they were linear or cyclic peptides, as well as according to the path from hormonally active cells to the target organ, in addition to their peptide analogs that can develop different treatments. Alternatively, an extensive reference survey was conducted for the peptides family "Neuropeptides" and some examples for this family that are chemically composed of various amino acids and peptides were studied.

Keywords: Amino Acid; Peptide Chemistry; Diseases; Neuropeptides

1. Introduction

During the last few years, the potential of amino acids and peptides and their derivatives as active ingredients for pharmaceuticals has been recognized, and considerable growth can be predicted [1-5]. Amino acids the building blocks of life are the letters of the alphabet that nature uses to construct words (peptides) and sentences (proteins). Linkage of individual amino acids occurs via the so-called peptide bond, which, as shown in figure (1), is formed by condensation of amine with carboxyl groups. Since amino acids are the monomer units for peptides and hence for proteins, many of the biologic properties are determined largely by the kinds of amino acids present, the order in which they are linked in a peptide or polypeptide chain, and the spatial relationship of one amino acid to another. Peptides are components of every living cell. They play an outstanding role in biochemistry as growth factors, hormones, ionophors, antibiotics, immune peptides, toxins, neuro peptides, antitumors...etc. There are a growing number of biological active peptides which have potential for the development of new therapeutics. However, native peptides are only rarely directly usable as drugs, due to inherent limitations which include rapid excretion by the liver and kidneys, and low oral activity. Furthermore,

peptides are often a selective in their actions owing to their flexible structures. In efforts to address these limitations, peptides are modified by several ways. Previously the scientists modified peptides into mimetics with specific physical, chemical and biological characteristics [6-8]. These so-called peptidomimetics are derived from peptides by partly or completely removing amid bonds while retaining essential amino acid side chains (such as -OH, -NH₂, -COOH, -SH, phenolic -OH, guanidine...etc) in a defined, spatial relationship. They can be developed in a rational design cycle from the parent peptide.

Jury Schreiber *et al.* [9] stated that the pharmaceutical application of some α -peptide is sometimes impossible due to their degradation by enzymes. β -peptides i.e. oligomers of β -amino acids, have recently been shown to form stable secondary structures [10-12]. β -peptides undergo no degradation [13], they can be considered for use as active substances in medicinal chemistry. They were used as sole carbon or nitrogen source for microorganisms. On the other hand we know that, living organisms synthesized proteins composed of L-amino acids. D-amino acids do occur in bacterial peptides, in peptide antibiotics; several peptides containing D-amino acids have also been isolated from

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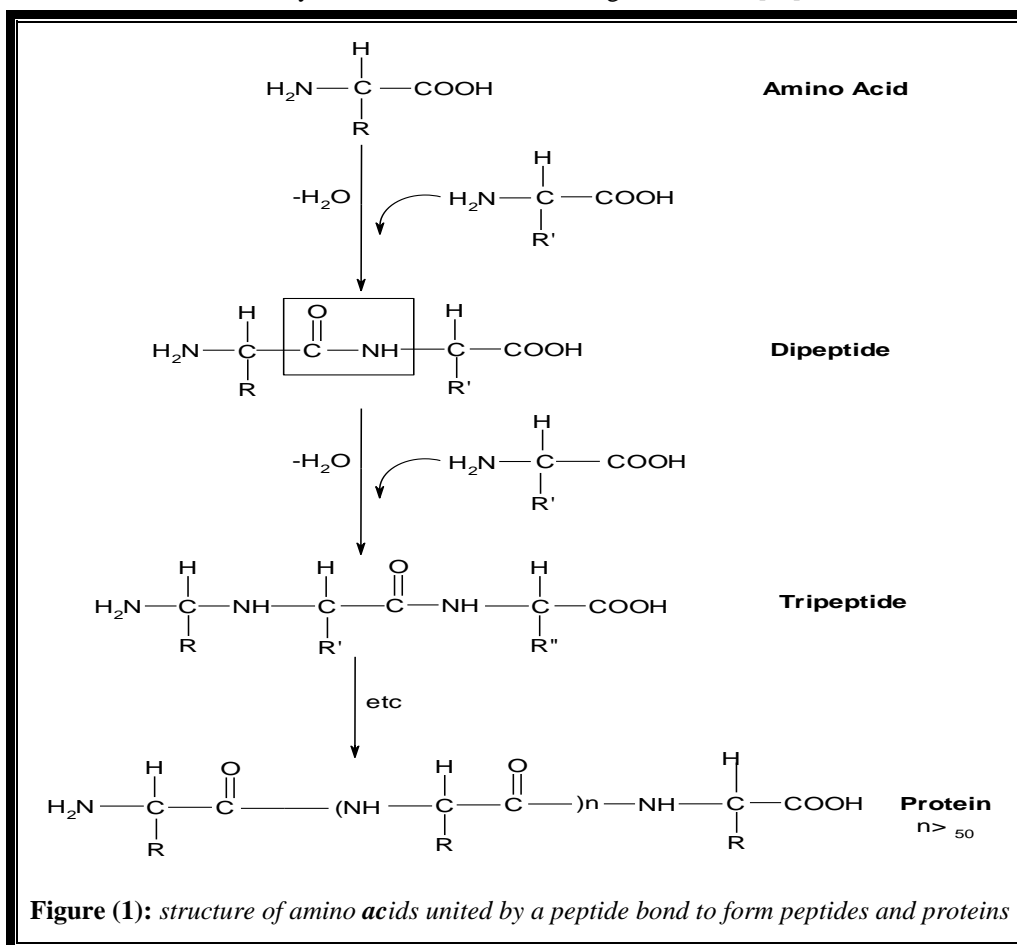
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invertebrates. D-amino acids are frequently used to prepare analogues containing the opposite absolute stereochemistry at one or more residues. The presence of D-amino acids may serve several

purposes, as the D-residue may modulate the biological activity of peptides by increasing their resistance to enzymatic attack and thereby prolong its biological half-life [14].



On the other hand, in general, it has been observed during our recent articles, that the synthetic organic and peptide chemistry are promising as biologically activate [15-43]. Recently [44], discoveries of new biologically active peptides rekindled the interest of many researchers in the peptide field, and began to explore new chemical modifications that would render peptides more suitable for medicinal use. In order to increase metabolic stability and absorption, various alterations of the backbone were introduced into peptide hormones and yielded novel analogues with prolonged activity *in vivo*, other modifications transformed substrates of proteinases (e.g. renin, thrombin) into potent transition-state analogues inhibitors which also possessed the stability and absorption characteristics of compound destined for clinical use. Due to this progress in the peptide field has led to the development of several novel peptide analogues of potential interest to medicine: receptor antagonists of the vasoconstrictor peptide endothelin,

sub-nanomolar inhibitors of pro-interleukin- $[\beta]$ -converting enzyme and of tissue kallikrein.

Although peptides still have, to some extent, little market potential within the sector of pharmaceutical chemistry, one can expect their use for therapeutic purposes to increase in the future in view of their importance as bioregulators.

Animal, plant, and bacterial cells contain a wide variety of low-molecular-weight polypeptides (3-100 amino acid residues) having profound physiologic activity. Some, including most mammalian polypeptide hormones, contain only peptide bonds formed between α -amino and α -carboxyl groups of the 20 L- α -amino acids present in proteins. However, additional amino acids or derivatives of the protein amino acids may also be present in polypeptides (though not in proteins). According to the mode of action of the peptide and the pathway from the hormone-active cells to the target organ, in addition to peptide analogues which have potential for the

development of therapeutics. The following peptide groups can be distinguished:

2. Neuropeptides:

They are peptides of the central nervous system, the biochemistry, physiology; pharmacology and synthesis of the Neuropeptides have been in the mainstream of research on vegetative and hormonal regulation in man and in animals.

2.1. Substance P:

In 1971 [45] Tregear, synthesized "Substance P" figure (2) which is a polypeptide consisting of 11-amino acid residues, and was discovered in the brain and the intestinal tract of man, mammals, and birds, as shown in figure (2). It has the effects of

stimulation of the smooth muscle and lowering of the blood pressure due to vasodilation. It plays a protective role against stress-determined disturbances. Niedrich, H. *et al.* [46] synthesized Sp derivative figure (3). This is one of the most active compounds in the vasodepressor- response test.

Also some substance P derivatives that contain D-amino acids e.g. [Arg⁶, D-Trp¹⁰]-sp (6-11) and [Pro⁴, D-Trp^{7,9}]-sp (4-11) act as strongly competitive antagonists [47]. Stavropoulos, George *et al.* [48], synthesized potent agonists of substance P. The analogues [Glp⁶, Glu(OBzl)¹¹]-sp(6-1 1) figure (4) and [Glp⁵, Glu(OBzl)¹¹]-SP-(5-1 1) figure (5) of the c-terminal hexapeptide and heptapeptide as shown in figures (4, 5). These peptide analogues are more potent than native SP itself.



Figure (2): structure of substance P



Figure (3): structure of substance P derivative



Figure (4): structure of substance P derivative the c-terminal hexapeptide and heptapeptide, sp (6-1 1)



Figure (5): structure of substance P derivative the c-terminal hexapeptide and heptapeptide, SP-(5-1 1)

2.2. Neurokinins

Neurokinins are peptides show a strong hypotensive effect like substance P. They were isolated from porcine spinal cord extracts and synthesized in 1984 by Munekata *et al.* [49]. They have the sequences figure (6, 7).

Calciagli, Valerio *et al.* [50] synthesized a new potent neurokinin A antagonist cyclic peptide figure (8), The prepared cyclic peptide analogue show very high potency and more active.

(Neurotensin NT) figure (9) is a 13-amino acid peptide, first isolated from bovin hypothalamus, also identified in the intestinal tract:

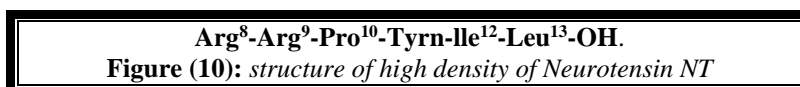
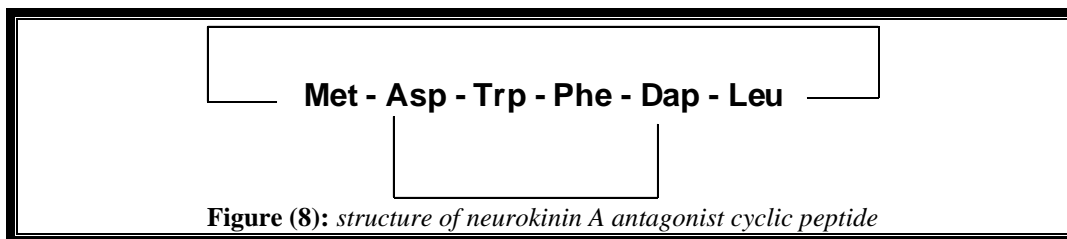
This hormone, causes lowering of the blood pressure, contracting action on the intestine and uterus, also increase the secretion of luteinizing hormone (LH) and follicle-stimulating hormone, glycoprotein (FSH) without influencing the release of somatotropin or thyrotropin. St-Pierre *et al.* [51] synthesized many NT fragments that are biologically active in the cardiovascular system. NT 8-13 shows the complete range of action of the native NT. Dirk Tourwe, *et al.* [52] synthesized a high density of neurotensin (NT) figure (10) receptors which is expressed on tumors like small cell lung carcinoma, colon- and pancreas carcinoma and meningiomas. For diagnosis of such type of cancers, the NT (8-13) sequence:



Figure (6): structure of sequences I of Neurokinins



Figure (7): structure of sequences II of Neurokinins



A series of analogues containing a Ψ ($\text{CH}_2\text{-NH}$) modification [53, 54] of $[\text{Arg}^8\text{-Arg}^9]$, $[\text{Lys}^8\text{-Arg}^9]$ or $[\text{Lys}^8\text{-Lys}^9]$ were prepared, as well as $[\text{N-Me-Arg}^8, \text{tLe}^{12}]$ and labelled. Koen Iterbeke *et al.* [55] also found that a radiohalogenated analogue of neurotensin (8-13), may be useful for the diagnosis of several tumors like small cell lung carcinoma, colon and pancreas carcinoma. Radioiodination and

selective radioiodination at Tyrⁿ were performed and studied [56, 57].

The first endogenous opioid peptides which are peptides with morphine-like activity were isolated from human and animal nerve tissue [58], they were $[\text{Met-Enkephalin}]$ figure (11) and $[\text{Leu-Enkephalin}]$ figure (12) and have the following structures:

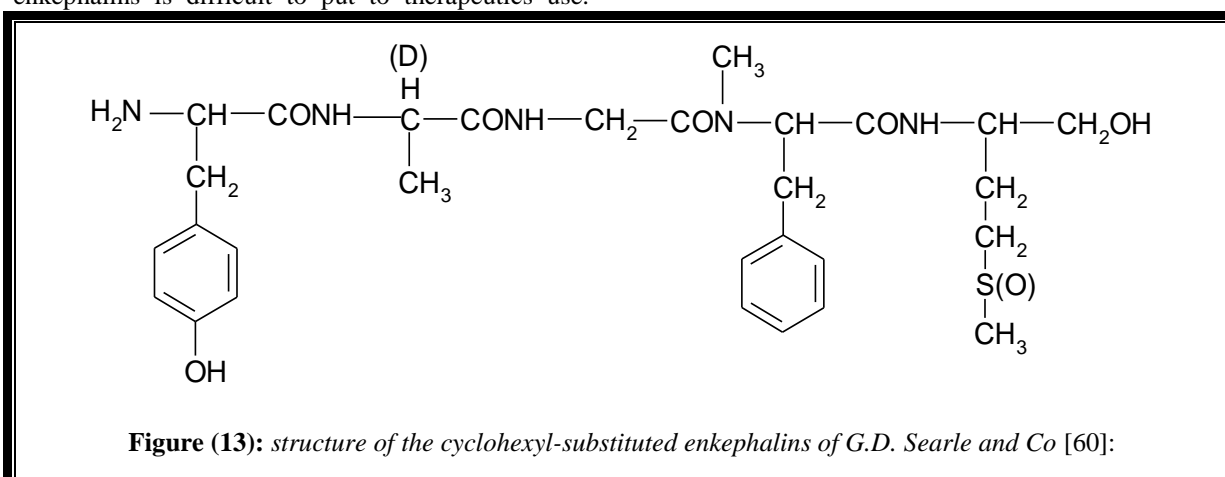


2.3. Enkephalins:

Enkephalins are found in varying amounts in nearly all regions of the nervous system, in the posterior lobe of the pituitary, and in the adrenal cortex. They play a role in the pain transmission in that they act as transmitters for the pain-inhibiting neurons in the spiral cord. Because of their peptide nature, the enkephalins is difficult to put to therapeutics use.

Many enkephalins derivatives have now been synthesized with increasing the analgesic effect with respect to enkephalin.

Pless, J. *et al.* [59] synthesized the following enkephalin derivative figure (13, 14), in which enzymatic degradation is blocked and has proved to be strongly analgesically active:



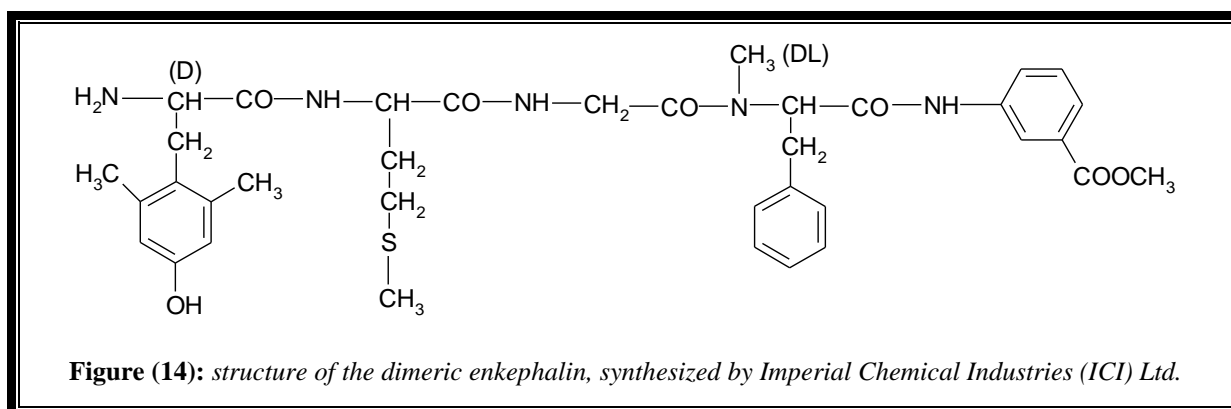
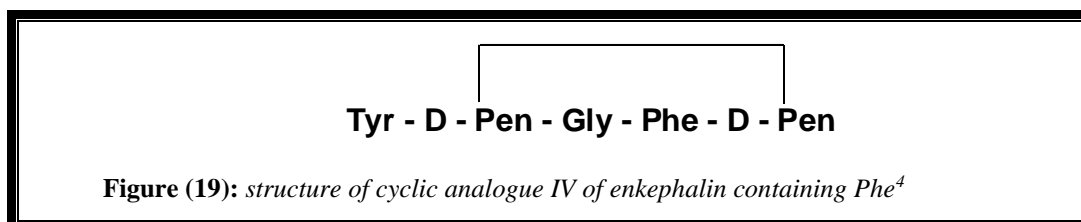
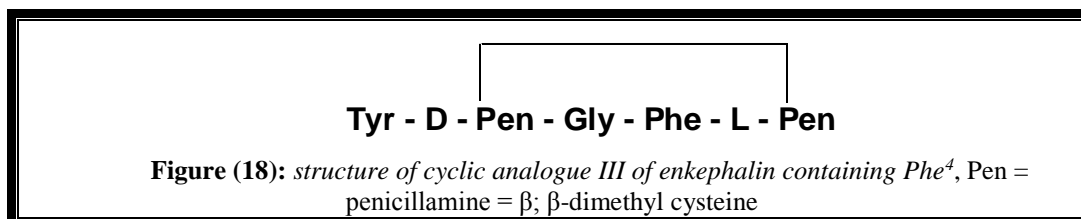
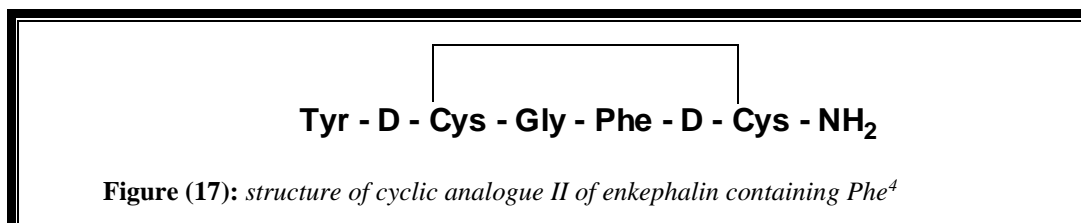
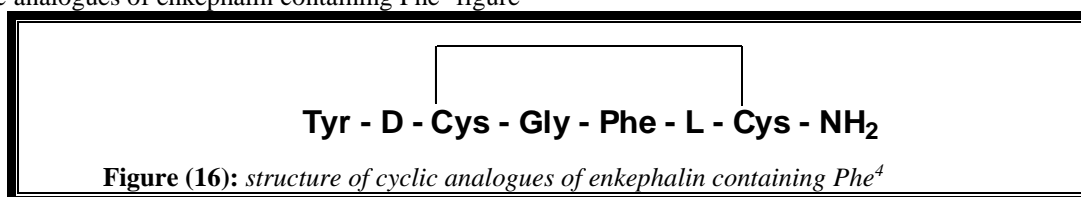


Figure (15): structure of enkephalin acts as a selective opiate-receptor antagonist [61]:

G.V. Nikiforovich *et al.* [62], synthesized four cyclic analogues of enkephalin containing Phe⁴ figure

(16-19), these peptides were studied and gave high analgesic effect.

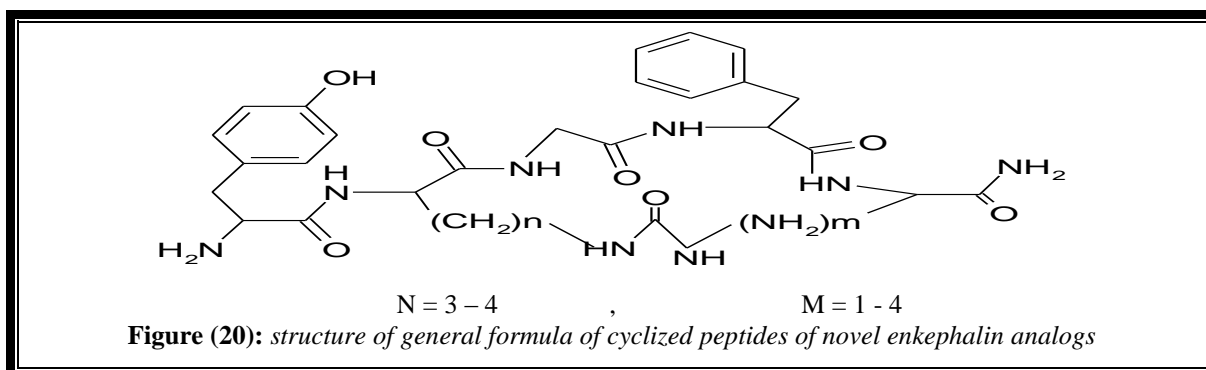


Recently reported [63] the synthesis and biological activity of a enkephalin analogue cyclized via a

ureido group incorporating the side-chain amino groups of two lysine residues, giving high analgesicity.

Danuta *et al.* [64], synthesized series of cyclized peptides of novel enkephalin analogs, for biological studies having the general formula figure (20).

Influence of the structural modifications was examined on the activity and selectivity, giving good data



Analogue to enkephalin, there is endorphins, both enkephalin and endorphin are a group of peptides which have been isolated from the pituitary. These peptides have higher analgesic potencies than morphine.

amino acid sequence and possessed morphine like activity [65]. The longest of these peptides, β -endorphin, a31-residue peptide (residues 61-91 of β -LPH), is about 20 to 50 times more potent than morphine as an analgesic and has a considerably longer duration of action than that of enkephalins.

Endorphins are long peptides were isolated from the intermediate lobe of the pituitary gland. The endorphins (α , β and γ) contained the met-enkephalin

Goldstein *et al.* [66, 67] isolated dynorphin, figure (21), which is 700 times as effective as Leu-enkephalin, from porcine pituitaries.



Figure (21): structure of dynorphin

G.P. Vlasov *et al.* [68], described novel approach for the design of peptides, fragments of 6-12 of dynorphin , [Ansyol-Arg⁶- Arg⁷-Ile⁸-Arg⁹-Pro¹⁰-Lysn-D-Leu¹²-NH₂], which was found to have anti-inflammatory activity, with the use of D,L-peptide

library approach, by using D- and L- derivatives of amino acids.

Dermorphin, figure (22), was isolated from the skin of the frog phyllomedusa sauvagei, exerts a strong analgesic effect and is 700 times as effective as morphin [69, 70]:

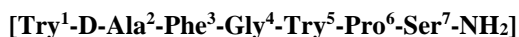


Figure (22): structure of dermorphin (naturally)

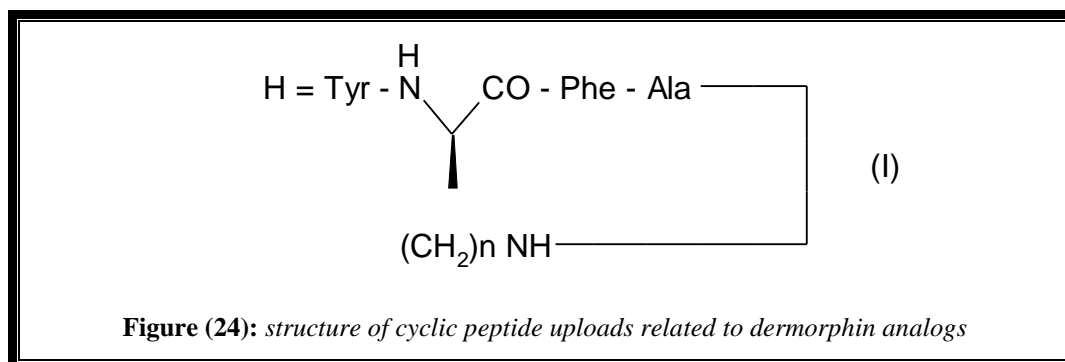
Synthetic dermorphin tetrapeptide, figure (23), and isomers synthesized by Tomatis *et al.* [71] are more effective than morphin or dermorphin itself.



Figure (23): structure of Synthetic dermorphin tetrapeptide

Ro, Seonggu *et al.* [72] continuing efforts to study structure-activity relationships (SAR) of peptide opioids, have resulted in the synthesis of series of cyclic peptide uploads related to dermorphin analogs,

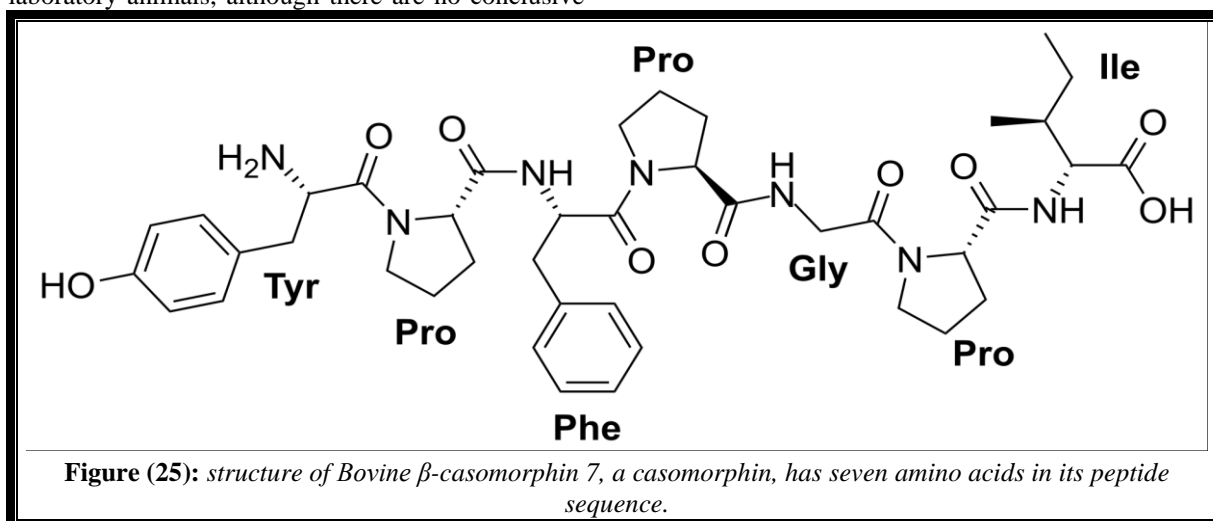
figure (24): where in series (I) ($n = 2-4$) incorporate 12-, 13-, and 14- membered rings, respectively. The biological activities of the prepared cyclic peptide opioids have been determined and showed highly active at both jx- and 5-opioid receptors.



2.4. Casomorphine:

Casomorphine, form (25): is an opioid peptide (a protein fragment) that has been shown to be derived from the digestion of milk protein casein [73]. Some digestive enzymes can completely break casein into peptides that have biological activity in cells and in laboratory animals, although there are no conclusive

causal effects in humans [73]. Moreover, although diverse research has shown high rates of use of complementary and alternative therapies for children with autism, including diets that exclude gluten and/or casein, on the other hand, as of 2008, there has been a lack of evidence that these different diets had no effects [74, 75].



From the naturally occurring ft-casomorphins the pentapeptide: [Try¹- Pro²-Phe³-Pro⁴-GIy⁵-(β -CM-5)], has been found to be the most potent analgesic compound [76]. The substitution of D-proline or D-pipecolic acid for L-proline⁴ in P-casomorphin-5, figure (26), led to high opioid activity and

preferential μ opiate receptor affinity compound: [Try-Pro-Phe-D-Pro-Gly], figure (27), produced a 700 times higher analgesic potency compared to the native β -casomorphin-5 and is 28 times more active than morphine [77, 78].



Figure (26): structure of P-casomorphin-5



Figure (27): structure of P-casomorphin-5 analog I

K. Neubert, *et al.* [79] started with the synthesis of cyclic analogues of β -casomorphin-5. The results of this study demonstrated that the introduction of α , w -diaminocarboxylic acid in the D-configuration into the 2-position of the β -casomorphin-5 produces a

remarkable increase of the analgesic potency, figure (28). The cyclization of the corresponding linear peptide resulted in a further enhancement of the analgesic action. Cyclic [D-orn²]- β -CM-5: [**Tyr-c (-D-Orn-Phe-Pro- Gly-)**] showed considerable analgesic effects.

Cyclic [D-orn²]- β -CM-5: [Tyr-c (-D-Orn-Phe-Pro- Gly-)]

Figure (28): structure of β -casomorphin-5 analog II α , w -diaminocarboxylic acid

2.5. Kyotorphin:

Kyotorphin which is analgesically active dipeptide Tyr-Arg, is supposedly causes secretion of Met-enkephalin (mentioned before). It was isolated from

bovine hypothalamus [80] as was the pentapeptide neo-kyotorphin (NK), figure (29), [81] [**Thr-Ser-Lys-Tyr-Arg**] which was isolated in 1982 from bovin brain.

[Thr-Ser-Lys-Tyr-Arg]

Figure (29): structure of the pentapeptide neo-kyotorphin (NK)

2.6. Thyrotropin-releasing hormone (TRH):

Mikhaleva, LI. *et al.* [82] isolated small peptides from the brain of hibernating. Yakutian ground squirrels. They traced a peptide which identical to neo-kyotorphin: [Thr-Ser-Lys-Tyr-Arg], and having analgesic activity. Their earlier experiments [83] with crude isolated fractions having pronounced pyrothermic and antimetabolic activity together with the ability to inhibit the slow voltage-sensitive calcium current. These lead to novel interesting hypothermic, antimetabolic and cardiotropic neuropeptides.

hormone production or inhibit release are low-molecular peptides in comparison with the anterior pituitary hormones and are present in certain areas of the hypothalamus.

Thyrotropin-releasing hormone (TRH), figure (30), was first isolated from sheep and porcine hypothalamus. It has the sequence: [Pyro Glu¹- His²- Pro³-NH₂]. Burgus *et al.* [84] synthesized (RTH) analog: [Pyro Glu¹-Met²-His³-Pro⁴-NH₂], figure (31), they found that its biological activity exceeds that of natural and synthetic TRH by factor of 10. TRH regulates the synthesis and the secretion of thyrotropin and prolactin and is used in the diagnosis and therapy of thyroid disorders.

The releasing hormones and the release-inhibiting hormones which stimulate the anterior pituitary into

[Pyro Glu¹- His²-Pro³-NH₂]

Figure (30): structure of thyrotropin-releasing hormone (TRH)

[Pyro Glu¹-Met²-His³-Pro⁴-NH₂]

Figure (31): structure of thyrotropin-releasing hormone (TRH), analog I

2.7. Gonadotropin-releasing Hormone (LH-RH):

Olson Gary L. *et al.* [85] designed and synthesized of peptide mimetics of thyrotropin-releasing hormone, in which the peptide backbone is entirely replaced by

a cyclohexane framework. The synthesized compound is found to be active; the mimetics are potent, active compounds, exhibiting oral activity. Other releasing hormone is Luteinizing Hormone or Gonadoliberin (Gonadotropin-releasing Hormone) (LH-RH): figure (32).

Pyro Glu¹-His²-Trp³-Ser⁴-Tyr⁵-Gly⁶-Leu⁷-Arg⁸-Pro⁹-Gly¹⁰-NH₂

Figure (32): structure of Gonadotropin-releasing Hormone (LH-RH)

Isolated from porcine and sheep hypothalamus tissue, possesses LH- releasing and FSH (follicle-stimulating hormone, glycoprotein) releasing activity and is available commercially as Luteal [86]. Stimulation of the secretion of LH (luteinizing hormone) in the female organism triggers ovulation and the formation of the corpus luteum responsible for the maintenance of pregnancy. The secretion of FSH stimulates the growth and the initial ripening of the follicle in the ovary and therefore sets in motion estrogen biosynthesis.

Many LH-RH analogs were synthesized having biological activity up to 30 times that of native substance e.g. buserelin [87]: figure (33), leuprorelin [88]: figure (34) and nafarelin [89]: figure (35), which, in comparison with native LH- RH, exert a 200-times stronger agonistic effect.

Buserelin came on the market as a nasal spray (suprefact) and Leuprorelin as (carcinil) as injectable product in 1984.

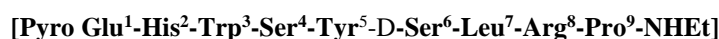


Figure (33): structure of Gonadotropin-releasing Hormone (LH-RH), analog I, buserelin

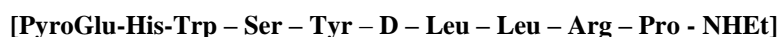


Figure (34): structure of Gonadotropin-releasing Hormone (LH-RH), analog II, leuprorelin



Figure (35): structure of Gonadotropin-releasing Hormone (LH-RH), analog III, nafarelin

Haviv, Fortuna *et al.* [90], synthesized N-terminus modified analogs of luteinizing hormone-releasing hormone (LH-RH). They prepared N-acyldecapeptides with general formula as shown in

figure (36), in which each letter changes to give different analogues.

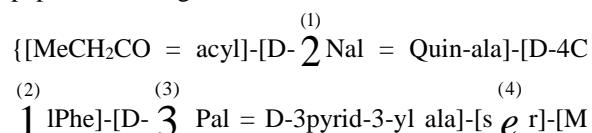


Figure (36): structure of Gonadotropin-releasing Hormone (LH-RH), analog IV, N-acyldecapeptides

2.8. Salmon GnRH and chicken GnRH II:

A total of 27 analogs were prepared and *in vitro* showed different activities. The following analog gave the highest results and more activity:

$[(\text{Me CH}_2\text{CO})\text{-D-2Nal}^1\text{-D-4Cl Phe}^2\text{-D-3Pal}^3\text{-Ser}^4\text{-MeTyr}^5\text{-D- Cit}^6\text{-Leu}^7\text{-Arg}^8\text{-Pro}^9\text{-D-Ala}^{10}\text{-NH}_2]$. This peptide analog can be detailed as follow:



(5)

e Tyr = Tyr (Me)-[D-Cit = citrul⁽⁶⁾ine]- Leu⁷-Arg⁸-Pro⁹-D-Ala¹⁰-NH₂}

In China, a synthetic analogues of Luteinizing hormone- Releasing Hormone (GnRH(LH-RH)), was used successfully for inducing fish ovulation.

Tomislav, *et al.* [91] prepared analogues of salmon GnRH and chicken GnRH II which has the common structure as shown in figure (37).



Figure (37): structure of analogues of salmon GnRH and chicken GnRH II

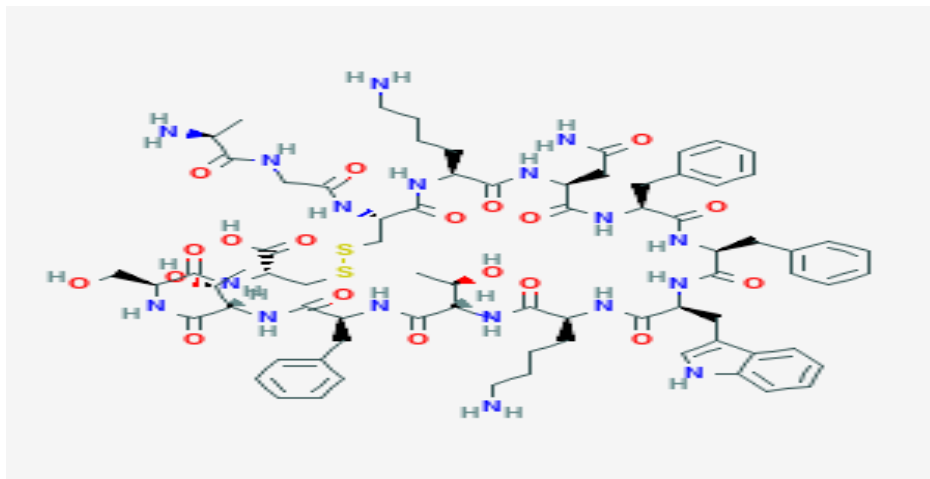
Where X and Y correspond to natural difference between molecules of salmon GnRH and chicken GnRH II, where as Z is either Pro- Gly-NH₂ OR

ProNHet. D-Orn was introduced into position 6 with the aim of increasing the potency of the analogues *in vivo* and also because the δ-amino group of this amino acid could be subjected to further

modifications. Peptides with C-terminal Gly NH₂ when applied in combination with pimozide, successfully induced ovulation in female African catfish. They increased the gonadotropin (GtH) level in golden caras.

2.9. Somatostatin (SST):

Another type of hormone of great interest and important functions is somatostatin (SST) (Growth Hormone-Re lease- inhibiting Hormone), figure (38),

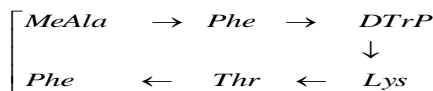


[Ala¹-Gly²-Cys³-Lys⁴-Asn⁵-Phe⁶-Phe⁷-Trp⁸-Lys⁹-Thr¹⁰-Phe¹¹-Thr¹²-Ser¹³-Cys]

Figure (38): structure of somatostatin (SST) (Growth Hormone-Re lease- inhibiting Hormone)

Somatostatin has attracted interest as regards therapeutic uses (treatment of diabetes mellitus, gastric ulcers and pancreatitis). Synthesis of its analogs has led to compounds that selectively inhibit the secretion of glucagon and insulin, exerting only a slight effect on the release of insulin and an intensified effect on the release of glucagon.

Cyclic hexapeptide analogs of SST inhibit the liberation of insulin, glucagon, and the growth hormone [92]:



Cyclic octapeptide SMS 201-995, figure (39), from Sandoz Ltd [93] has a longer duration of action than native SST and inhibits the secretion of GH more selectively. Moreover, it enhances the hypoglycemic effect of insulin while simultaneously decreasing glucagon.

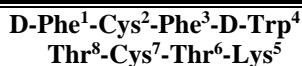


Figure (39): structure of cyclic octapeptide SMS 201-995

2.10. Proteohormones:

Another family of hormones are Proteohormones of the pituitary (Hypophysis). As a rule, a hypothalamic hormone should always control a hormone in the anterior pituitary. The pituitary hormones (e.g. follicle - stimulating hormone, prolactin or

thyrotropin) are then transported through the bloodstream to the secondary target organs, where, for example, they stimulate the production of corticosteroids in the adrenals or the formation of thyroxine in the thyroid.

Somatotropin (Growth hormone) [STH] or the human growth hormone (HGH) is a linear peptide hormone made up of 191 amino acids with 2 intrachain disulfide bridges, it is found in high concentration in the pituitary which is much higher than other pituitary hormones. It has some of the actions of lactogenic hormone (Prolactin) and of human placental lactogen. They have significant degree of immunologic and biologic cross-reactivity. It is found that, excessive secretion of HGH in the growing years leads to gigantism. HGH also used in cases of muscular dystrophy, bone dicalcification (osteoporosis) and hemorrhagic gastric ulcers [94-96].

Corticotropin (ACTH), exerts its major action on the adrenal cortex, promoting steroid synthesis by

Ser-Tyr-Ser-Met-Glu⁵-His-Phe-Arg-Trp-Gly¹⁰-Lys-Pro-Val-Gly-Lys¹⁵-Lys-Arg-Arg-Pro-Val²⁰-Lys-Val-Tyr-Pro-Asn²⁵-Gly-Aia-Gly-Asp-Glu³⁰-Ser³¹-Ala³²-Glu³³-Ala-Phe³⁵-Pro-Leu-Gly-Phe

Figure (40): structure of corticotropin (ACTH), analog I, Human

Ser-Tyr-Ser-Met-Glu⁵-His-Phe-Arg-Trp-Gly¹⁰-Lys-Pro-Val-Gly-Lys¹⁵-Lys-Arg-Arg-Pro-Val²⁰-Lys-Val-Tyr-Pro-Asn²⁵-Gly-Aia-Gly-Asp-Glu³⁰-Leu³¹-Ala³²-Glu³³-Ala-Phe³⁵-Pro-Leu-Gly-Phe

Figure (41): structure of corticotropin (ACTH), analog II, Porcine

Ser-Tyr-Ser-Met-Glu⁵-His-Phe-Arg-Trp-Gly¹⁰-Lys-Pro-Val-Gly-Lys¹⁵-Lys-Arg-Arg-Pro-Val²⁰-Lys-Val-Tyr-Pro-Asn²⁵-Gly-Aia-Gly-Asp-Glu³⁰-Ser³¹-Ala³²-Gln³³-Ala-Phe³⁵-Pro-Leu-Gly-Phe

Figure (42): structure of corticotropin (ACTH), analog II, Bovine

Oxytocin, figure (43) and vasopressin, figure (44) are two peptide hormones among the best-researched active peptide substances. The actual site of formation of oxytocin and vasopressin is in the

hypothalamus, from which the two peptides are carried to the posterior pituitary bound to neurophysins (transport proteins) and stored. The structure and synthesis of oxytocin and vasopressin were worked out by du Vigneaud *et al.* [97]:

Cys¹-Tyr²-He³-Gin⁴-Asn⁵-Cys⁶-Pro⁷-Leu⁸-Gly⁹-NH₂

Figure (43): structure of oxytocin

Cys¹-Tyr²-Phe³-GIn⁴-Asn⁵-Cys⁶-Pro⁷-Arg⁸-Gly⁹-NH₂

Figure (44): structure of vasopressin

Oxytocin is increased during labor; it causes uterine contraction and is employed in obstetrics when induction of uterine contraction is desired. Also it causes contraction of the smooth muscles in the mammary gland, resulting in milk excretion.

On the other hand vasopressin is similar to that of oxytocin. The differences are in 2 amino acids: a) Isoleucine in oxytocine replaced by Phe in vasopressin. b) Leucine of oxytocine replaced by lys or Arg. depending on the origin of vasopressin.

The vasopressins cause reabsorption of water by increasing renal permeability, thus concentrating the primary urine, with high doses of vasopressin the blood pressure and the intestinal peristalsis are increased. More than 350 oxytocine and vasopressin analogues have been reported in the literature.

Recently, many analogues of oxytocine were synthesized. Masushima *et al.* [98] isolated peptide amide from *E. Foetida*, This peptide is an oxytocin-

like peptide, enhances spontaneous contraction of a digestive tract of *E. foetida*, has activity for starting the contraction movement of a kidney tube of *E. foetida*, and not only is useful as a biochemical reagent but also provides a new approach to a drug and agrochemistry. This peptide has the sequence as shown in figure (45). Zdenko Prochazka, *et al.* [98] synthesized eight new analogs of oxytocin receptor molecule figure (46).



Figure (45): structure of oxytocine, analog II



X = L- or D-Phe (P-Ph), = L- or D-Phe (Penta-Me), = L- or D-Phe (P-tBu) L- or D-Phe (P-TFM)

Phe (P-Ph) = P-phenyl phenylalanine, Phe (Penta-Me) = 2, 3, 4, 5, 6-pentamethylphenylalanine, Phe (P-tBu) = P-tert-butyl phenylalanine, Phe (P-TFM) = P-trifluoromethyl phenylalanine.

Figure (46): structure of oxytocin, eight analogs

All analogs were found to be inhibitors of oxytocine action in the uterus *in vitro* and *in vivo* tests. Jiri Velek, *et al.* [99] studied the formation and effects of pyroglutamic hexapeptide and pentapeptide metabolites of oxytosin (OT) and vasopressin (VP) in the brain and the transport of peptides from the brain to the target tissues and, vice versa. They prepared analogs of pyroglutamic hexapeptides derived from OT, VP and [D-Arg] vasopressin (DVP) with L-orn

in position 6 of amino acid sequence of the native peptides. The analogues had the following structure: P-Glu-Asn-Orn-Pro-X-Gly-NH₂, where X = Leu, Arg or D-Arg. The prepared peptides were tested according to their effects on the learning precesses and memory of rats which had amnesia.

Jirina *et al.* [100] synthesized different analogues of arginine- vasopressin which has the formula, figure (47).

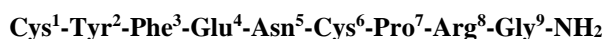


Figure (47): structure of analogues of arginine- vasopressin

Four vasopressin analogs modified in position 3 with (3-thienyl alanine were prepared and its biological activity were studied, figure (48).

Vilhard, Hans *et al.* [101] showed that the replacement of L-Tyr by L-Tyr (Me), L- or D-Phe

(PMe), L- or D-Phe (PEt) in combination with substitution of D-arginine by D-homoarginine, resulted in activation of its effects. Mizuochi, Tokiko *et al.* [102-104] synthesized the following peptide, which is useful for treating diseases of brain nerve functions such as senile dementia, Alzheimer-type dementia, and brain nerve disorders.



Figure (48): structure of vasopressin

Vasopressin released within the brain may have several actions:

Vasopressin is released into the brain in a circadian rhythm by neurons of the suprachiasmatic nucleus [105]. Vasopressin released from posterior pituitary is associated with nausea [106]. Recent evidence

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