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REVIEW

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Role of food-derived opioid peptides in the central nervous and gastrointestinal systems

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Abstract

Opioid receptors are widely distributed in central nervous system and peripheral tissues. Endogenous opioid receptor ligands are involved in many physiological processes. Exogenous peptides, derived from food proteins with gastrointestinal proteases, also exert opioid-like activities, and they include gluten exorphins (wheat), casomorphins (milk), rubiscolins (spinach), and soymorphins (soybean). Milk-derived opioid peptides play both agonistic and antagonistic roles, and most of the opioid peptides exert regulatory functions in the central nervous system, related to nociception, emotion and memory after oral, intracerebroventricular, or intraperitoneal administration. This indicates that the peptides may have crossed the blood-brain barrier or acted peripherally. Furthermore, some food-derived opioid peptides influence gastrointestinal functions such as gut motility, hormone release, appetite, mucus production, and local immunity. In healthy states, food-derived opioid peptides could benefit both the nervous and digestive systems, whereas in pathological conditions, the gastrointestinal permeability change and opioid excess may contribute to pathogenesis of some disorders.

Practical applications

Opioid receptors are important biological targets for the treatment of multiple diseases. Traditional opiate compounds, such as alkaloids, are demonstrated to exert numerous side effects, thereby limiting their clinical effectiveness. It is thought that food-derived opioid peptides may be safer than the alkaloids, and therefore can be applied in functional food development. In this review, we summarized the already discovered food opioid peptides from different sources, and elaborated their physiological functions on the central nervous and gastrointestinal systems. These effects support further exploration of the opioid peptides as therapeutic agents or as functional food ingredient for human health promotion.

KEYWORDS

casomorphins, central nervous system, exorphins, food peptides, gastrointestinal tract, opioid peptides, rubiscolins, soymorphins

1 | ENDOGENOUS OPIOID SYSTEM

Endogenous opioid system is composed of several opioid receptors and the corresponding endogenous ligands, both of which are distributed throughout the body and considered to be involved in a variety of physiological processes, not only in the nervous, but also numerous non-nervous systems, such as the gastrointestinal tract.

1.1 | Opioid receptors

As early as 1973, the existence of receptors for opiate drugs in the brain had been documented (Akil et al., 1998). Later in the 1990s, three major subtypes of opioid receptors, δ-, κ-, and μ-opioid receptors (encoded by *Oprd1*, *Oprk1*, and *Oprm1* gene, respectively) were cloned, leading to a better understanding of their molecular and pharmacological characteristics (Akil et al., 1998). More recently, a new receptor named opioid receptor-like 1 (ORL1, gene symbol *Orl1*) was discovered as the fourth opioid receptor, and it binds endogenous neuropeptides nociceptin and orphanin FQ, and only shows low affinity for standard opiates (Toll, Bruchas, Calo, Cox, & Zaveri, 2016).

All the four opioid receptors are members of the G protein-coupled receptor (GPCR) superfamily, and share a common structure of seven transmembrane domains. Opioid receptors are coupled to $G_{i/o}$ proteins, which consists of three (α, β, and γ) subunits. When recognized by its ligand, the heterotrimeric GPCR of opioid dissociates into G_{α} and $G_{\beta\gamma}$ subunits, which is followed by G_{α} translocation and inhibition of adenylyl cyclase activity, and modulation of ion (K^+, Ca^{2+}) influx (Law, Wong, & Loh, 2000). Additionally, opioid receptors engagement can also activate downstream phospholipase Cβ (PLCβ) and mitogen-activated protein kinase (MAPK) pathways (Law et al., 2000).

1.2 | Endogenous opioid peptides

The first endogenous ligands for opioid receptors was identified in 1975 by Hughes et al. (1975) and was named as enkephalins, which includes Met- and Leu-enkephalin, manifesting as identical sequences of Tyr-Gly-Gly-Phe-X, but with a different amino acid residue (Met or Leu) at position X. Thereafter, a series of endogenous opioid peptides, named endorphins, dynorphins, and endomorphins, were discovered. Most of the peptides are proteolytic cleavage products derived from large protein precursors. For example, proopiomelanocortin (POMC) is the precursor of endorphins and some other non-opioid peptides such as adrenocorticotropic hormone (ACTH), a stress-related hormone. Similarly, dynorphins and neomorphins are derived from prodynorphin (PDYN), and enkephalins are derived from proenkephalin (PENK). With the exception of endomorphins, all opioid peptides share a common sequence of Tyr-Gly-Gly-Phe at the N-terminus, which is now considered as an important opioid motif (Sobczak, Sałaga, Storr, & Fichna, 2014).

Each precursor family displays an affinity for a specific opioid receptor subtype. Dynorphin displays high selectivity for κ-opioid receptor, while Leu-enkephalin and β-endorphin are more selective for δ- and μ- receptors, respectively (Akil et al., 1998). The ORL1 ligands, nociceptin and orphanin FQ, which are derived from pronociceptin/OFQ, show high sequence homology to dynorphin A, with only a slight modification in the opioid motif, i.e., Phe replaces Tyr at the N-terminus. This substitution prevents nociceptin/orphanin FQ from interacting with other opioid receptors (Hughes et al., 1975), thereby enhancing their specificity.

2 | FOOD-DERIVED OPIOID PEPTIDES

Due to structural similarity to endogenous opioids, dietary proteins can be important sources of opioids. Accumulating evidence demonstrates that peptides derived from enzymatic hydrolysis of food proteins (Table 1) could be recognized by opioid receptors, and display opioid-like molecular and physiological activities.

2.1 | Opioid peptides derived from wheat

In 1979, Zioudrou et al. first described that peptides purified from pepsin-hydrolyzed wheat gluten and milk α-casein can act as opioid receptor agonists, named exorphins because they are exogenous and have morphine-like activity (Zioudrou, Streaty, & Klee, 1979). Subsequently, in 1992 and 1993, Fukudome and Yoshikawa further revealed the structural information of the gluten exorphins, and five subtypes were identified consisting of gluten exorphin A4 (Gly-Tyr-Tyr-Pro), A5 (Gly-Tyr-Tyr-Pro-Thr), B4 (Tyr-Gly-Gly-Trp), B5 (Tyr-Gly-Gly-Trp-Leu), and C (Tyr-Pro-Ile-Ser-Leu). All the peptides were determined to have opioid activity on the basis of electrically stimulated guinea pig ileum (GPI) and mouse vas deferens (MVD) tests, and by radio-receptor assay, which evaluates their selectivity to opioid receptors. Except for gluten exorphin C, which showed higher affinity to μ-opioid receptor, gluten exorphin A/B were considered to be δ-selective, and the B5 subtype, which corresponds to [Trp^4, Leu^5]-enkephalin, showed the most potent opioid activity among the peptides (Fukudome & Yoshikawa, 1992, 1993).

Gluten is the major wheat protein complex and is composed of glutenins and gliadins. The sequence of gluten exorphin A is reported to be derived from the primary structure of the high-molecular-weight glutenin (Fukudome & Yoshikawa, 1992). Moreover, gliadorphin-7 (or gliadinomorphin-7, Tyr-Pro-Gln-Pro-Gln-Pro-Phe), which is derived from α-gliadin, also shows opioid activity (Pruimboom & de Punder, 2015). However, the sequences of gluten exorphin B and C were not found in any known sequence of gliadin or glutenin, suggesting that they are possibly derived from other unknown wheat proteins (Fukudome & Yoshikawa, 1992, 1993).

2.2 | Opioid peptides derived from milk

Milk proteins contain two major groups, caseins and whey. Caseins, which include the α_{s1}, α_{s2}, β, and γ subtypes, comprise about 80% of bovine milk proteins and 20%–45% of human milk. The first identified opioid peptides are β_b-casomorphin-7 (Tyr-Pro-Phe-Pro-Gly-Pro-Ile), from bovine β-casein, and its analogs, as well as β_b-casomorphin-4, -5

TABLE 1 Examples of food-derived opioid peptides

Opioid peptide	Source	Sequence
β_b-casomorphin-4	bovine milk β-casein	YPFP
β_b-casomorphin-5		YPFPG
β_b-casomorphin-6		YPFPGP
β_b-casomorphin-7		YPFPGPI
β_b-casomorphin-8		YPFPGPIP/H
neocasomorphin-6		YPVEPF
α_b-casein exorphin (1-7)	bovine milk α-casein	RYLGYLE
α_b-casein exorphin (2-7)		YLGYLE
casoxin A	bovine milk κ-casein	YPSYGLN
casoxin B		YPYY
casoxin C		YIPIQYVLSR
α_b-lactorphin	bovine milk α-lactalbumin	YGLF-NH2
β_b-lactorphin	bovine milk β-lactoglobulin	YLLF-NH2
βh-casomorphin-4	human milk β-casein	YPFV
βh-casomorphin-5		YPFVE
βh-casomorphin-7		YPFVEPI
βh-casomorphin-8		YPFVEPIP
casoxin D	human milk α-casein	YVPFPPF
α_h-casomorphin		YVPFP
α_h-lactorphin	human milk lactalbumin	YGLF-NH2
lactoferrsoxin A	bovine/bovine milk lactoferrin	YLGSGY-OCH3
lactoferroxin B		RYYGY-OCH3
lactoferroxin C		KYLGPQYOCH3
gluten exorphin A5	wheat HMW glutenin	GYYPT
gluten exorphin A4		GYYP
gluten exorphin B5		YGGWL
gluten exorphin B4		YGGW
gluten exorphin C		YPISL
gliadorphin-7	wheat α-gliadin	YPQPQPF
rubiscolin-5	spinach RuBisCo	YPLDL
rubiscolin-6		YPLDLF
soymorphin-5	soy β-conglycinin	YPFVV
soymorphin-6		YPFVVN
soymorphin-7		YPFVVNA
hemorphin-6	bovine hemoglobin	YPWTQR
oryzatensin	rice soluble protein	GYPMYPLPR

Notes. Table was modified from the publication by Garg et al. (2016); HMW, high molecular weight; RuBisCo, ribulose-1,5-bisphosphate carboxylase/oxygenase

and -6, which are derived by sequential removal of three, two or one amino acid residues, respectively from the C-terminus of β_b-casomorphin-7 (Brantl, Teschemacher, Bläsig, Henschen, & Lottspeich, 1981). Among them, β_b-casomorphin-5 showed the most potency in the GPI and MVD opioid activity assays (Brantl et al., 1981). Fragments with similar sequence, named as β_h-casomorphins, have been identified from human milk enzymatic digests and have been established for their opioid agonistic effects (Koch, Wiedemann, & Teschemacher, 1985). Moreover, some α-casein-derived peptides were also demonstrated as opioid agonists, and these include α_b-casein exorphins ((Arg)-Tyr-Leu-Gly-Tyr-Leu-Glu) from bovine α-casein and α_h-casomorphin (Tyr-Val-Pro-Phe-Pro) from human α-casein (Teschemacher, Koch, & Brantl, 1997).

Whey consists of α-lactalbumin, β-lactoglobulin, immunoglobulins, serum albumin, and minor proteins such as lactoperoxidase, lactoferrin, etc. Fragments corresponding to whey proteins were reported to exert opioid-like activity, such as α_b-lactorphin (Tyr-Gly-Leu-Phe-NH_2, with amidated C-terminal) from bovine α_b-lactalbumin

and β_b-lactorphin (Tyr-Leu-Leu-Phe-NH_2) from bovine β_b-lactoglobulin, although both peptides only show low affinity for opioid receptors, and weak effects in the GPI assay (Garg, Nurgali, & Mishra, 2016; Teschemacher et al., 1997).

On the other hand, some enzymatic digests of milk protein are considered to act as antagonists of opioid receptors. Such peptides include casoxin A (Tyr-Pro-Ser-Tyr-Gly-Leu-Asn-Tyr), B (Tyr-Pro-Tyr-Tyr), and C (Tyr-Ile-Pro-Ile-Gln-Tyr-Val-Leu-Ser-Arg) from bovine κ-casein, and casoxin D (Tyr-Val-Pro-Phe-Pro-Pro-Phe) from human α-casein (Garg et al., 2016; Teschemacher et al., 1997). Besides, synthesized human lactoferrin fragments, lactoferroxin A (Tyr-Leu-Gly-Ser-Gly-Tyr-OCH_3, with methoxylated C-terminal), B (Arg-Tyr-Tyr-Gly-Tyr-OCH_3), and C (Lys-Tyr-Leu-Gly-Pro-Gln-Tyr-OCH_3) were also found to show moderate activities as opioid antagonists, similar to the effect of casoxins (Garg et al., 2016). Most milk-derived opioid peptides are considered to be selective for μ-opioid receptor, except for casoxin D, which only shows weak affinity to opioid receptors, but antagonized the effect of both μ- and δ-opioid agonist equally in the GPI and MVD assays (Teschemacher et al., 1997).

2.3 | Rubiscolins, soymorphins, and other food-derived opioid peptides

Rubiscolins were first discovered as food-derived opioid peptides in 2001 from pepsin digests of spinach D-ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCo) (Yang et al., 2001), which is a major protein in green plant leaves, and thus a ubiquitous food source for most populations. Two peptides, rubiscolin-5 (Tyr-Pro-Leu-Asp-Leu) and -6 (Tyr-Pro-Leu-Asp-Leu-Phe), were identified to be selective for δ-opioid receptor in [^{3}H] deltorphin II-binding assay, and they also showed potent opioid-like activity in the MVD assay (Yang et al., 2001). Relatively, rubiscolin-6 showed a higher affinity for the receptor and opioid activity. The rubiscolin-6 sequence is conserved in the large RuBisCo subunit in most of higher plants. Interestingly, modification of rubiscolin-6 to Tyr-Pro-Ile-Asp-Leu-Phe (substitution of Leu-3 with Ile), enhanced the potency in δ opioid activity (Yang, Sonoda, Chen, & Yoshikawa, 2003). The new structure was found to exist naturally in some algae, such as *Euglena stellata*, *Euglena gracilis* and *Mesostigma viride*, suggesting that more active δ opioid peptides can be obtained from algal-based food.

In contrast, soymorphins are synthesized peptides based on the amino acid sequence Tyr-Pro-Phe-Val found in the soy β-conglycinin β-subunit, which is similar to the structure of human β_h-casomorphin-4. Peptides Tyr-Pro-Phe-Val-Val, Tyr-Pro-Phe-Val-Val-Asn, and Tyr-Pro-Phe-Val-Val-Asn-Ala were named as soymorphins-5, -6, and -7, respectively. Soymorphins were considered to be specific ligands of μ-opioid receptor, and soymorphins-5 showed the highest opioid activity of the three peptides (Ohinata, Agui, & Yoshikawa, 2007). Release of adequate amounts of the soy peptides by enzymatic hydrolysis is needed to fully assess their potential as food-derived opioid-like peptides. Other relatively less explored opioid peptides have been reported, including hemorphin-6 (Tyr-Pro-Trp-Thr-Gln-Arg) derived from bovine hemoglobin (Artemova, Bumagina, Kasakov, Shubin, & Gurvits, 2010) and oryzatensin (Gly-Tyr-Pro-Met-Tyr-Pro-Leu-Pro-Arg) derived from rice soluble protein (Takahashi, Moriguchi, Yoshikawa, & Sasaki, 1994).

3 | FUNCTIONS OF FOOD-DERIVED OPIOID PEPTIDES IN THE CENTRAL NERVOUS SYSTEM

In context of the critical role of opioidergic neurons in the central nervous system, food-derived opioid peptides have received a lot of attention in the area of behavior control. Particularly, the effects of β-casomorphin in nociception, spontaneous behavior, and memory are well documented.

By using multiple nociceptive models, including current-induced vocalization test, hot plate test, and tail flick test, the analgesic effect of β-casomorphins (-3, -4, -5, -6, and -7) were evaluated by intracerebral (*i.c.*) or intracerebroventricular (*i.c.v*) routes. Though obtained from different research groups, the conclusions from the study results were largely unanimous. With the exception of β-casomorphin-3, all the β-casomorphins were reported to decrease pain in the animals, and this effect was blocked with opioid antagonists, such as naloxone. Among them, β-casomorphin-5 exerted the highest analgesic effect (Lister, Fletcher, Nobrega, & Remington, 2015). Moreover, injection of β-casomorphin-5 (*i.c.v*) at a high dose of 10 mg decreased the step-down latency of mouse passive avoidance model, indicating its influence on learning and memory progress (Sakaguchi, Koseki, Wakamatsu, & Matsumura, 2003). Moreover, β-casomorphins were reported to be involved in modulating other behaviors such as locomotion and anxiety (Lister et al., 2015).

It is noteworthy that intraperitoneal (*i.p.*) β-casomorphin-5 and −7 were also reported to reduce nociception in rat pups and adults, respectively (Blass & Blom, 1996; Lister et al., 2015), supporting a possibility of these peptides, or their active fragments, to cross the blood brain barrier. Whether casomorphin administration by oral route (*p.o.*) could show a regulatory function in the central nervous system is still unknown. However, many studies demonstrated that the half-life of casomorphins in plasma was short, due to their degradation by prolyl dipeptidyl peptidase IV (DPP-IV), which cleaves the dipeptide fragment from the N-terminus after the proline residue.

On the other hand, oral administration of rubiscolin-6 to mice was capable of exhibiting an anxiolytic effect mediated by dopamine D1 and σ1 receptors (Hirata et al., 2007). Moreover, soymorphin-5 (*p.o.*) showed a similar effect in mice, which led to an increase in the time the mice stayed in open arms during elevated plus-maze test (Yoshikawa, 2015). Moreover, rubiscolin-6 administration was able to enhance the memory consolidation and reduce nociception in mice as well (Lister et al., 2015; Perlikowska & Janecka, 2017; Yang, Kawamura, & Yoshikawa, 2003). However, gliadorphin-7, even by intravenous (*i.v.*) administration, failed to induce any behavioral changes in normal rats (Sun & Cade, 2003), suggesting its inability to reach the brain by systemic delivery.

4 | FUNCTIONS OF FOOD-DERIVED OPIOID PEPTIDES IN THE GASTROINTESTINAL TRACT

Besides the central nervous system, food-derived opioid peptides can also act locally to influence gastrointestinal functions. Opioid system is an attractive pharmacological target for gastrointestinal disorders. Opioid agonist, such as loperamide, is widely used for clinical diarrhea control, due to its role in relaxation of intestinal smooth muscles through cyclic adenosine monophosphate-dependent protein kinase A (cAMP-PKA) signaling pathway. Similarly, food-derived opioid peptides also show potency in regulation of gastrointestinal motility. For instance, gluten exorphins were reported to prolong intestinal transit time, and this effect was reversed using a combined treatment with opioid receptor antagonist, naloxone (Morley et al., 1983). Moreover, oral administration of casein hydrolysates or β-casomorphin-5 was found to delay gastrointestinal transit in rats (Daniel, Vohwinkel, & Rehner, 1990), and inhibit colonic propagating contractions by blocking cholinergic neurotransmission in vitro (Dalziel et al., 2014). Similar findings were also reported for soymorphins, which decreased gut motility in mice, after oral administration (Kaneko, Iwasaki, Yoshikawa, & Ohinata, 2010). Using specific gut receptor antagonists, the soy peptides were found to decrease small intestinal transit *via* the μ1 opioid receptor in combination with the serotonin 1A receptor, dopamine receptor D2, and γ-aminobutyric acid type B receptor-activated systems (Kaneko et al., 2010). Notably, these gut activities of soymorphins resulted in a dose-dependent decrease in food intake (anorexigenic activity) in the mice. On the other hand, for opioid antagonistic peptides, casoxin-4 (Tyr-Pro-Ser-Tyr-OCH3, a truncated peptide from casoxin A) showed a capability of reversing morphine-induced inhibition of mouse and guinea pigs ileal contraction in vitro, although it failed to influence morphine-inhibited mouse small intestinal transit by oral route (Patten, Head, & Abeywardena, 2011). In addition, casomorphins also exhibited antidiarrhea effect through stimulating the absorption of electrolytes and water in the small intestine (Tomé, Ben Mansour, Hautefeuille, Dumontier, & Desjeux, 1988).

Moreover, food-derived opioid peptides could affect gastrointestinal hormone secretions. Hydrolysates of gluten were reported to cause a naloxone-reversible increase in plasma somatostatin-like activity (Morley et al., 1983). Conversely, long-term administration with β-casomorphin-7 decreased the expression of somatostatin in rats (Zong, Chen, Zhang, & Zou, 2007). Somatostatin is a crucial inhibitory hormone in regulating various hormones, including other gastrointestinal hormones, insulin and growth hormone. In addition, somatostatin plays an important role in appetite regulation. Indeed, both casomorphins and rubiscolin-6 were reported to stimulate food intake in experimental animals, and this action is likely mediated by the gastrointestinal or hepatic receptors, which transmit messages to the brain *via* the afferent vagus nervous (Perlikowska & Janecka, 2017).

Many studies have demonstrated that β-casomorphin-7 is a strong inducer of intestinal mucus, and thereby influences the integrity of the intestinal barrier. In DHE cells, a rat mucin-producing cell line, β-casomorphin-7 acted directly in raising Muc2 and Muc3 protein expressions, while in human goblet cells, HT29-MTX, it increased Muc5AC mRNA expression significantly (Zoghbi et al., 2006). Moreover, experiments using isolated rat jejunum with vascular perfusion showed that β-casomorphin-7 was capable of inducing a naloxone-reversible secretion of mucin, by both luminal and intra-arterial administration (Claustre et al., 2002). Besides, several other food-derived opioid peptides were also found to promote intestinal mucin production, based on HT29-MTX cell screening assay, and the peptides include neocasomorphin, β_h-casomorphin-5, α_b-casein exorphin, β_b-lactorphin, α-lactorphin, and gluten exorphin A5 (Martínez-Maqueda et al., 2012). Additionally, like other opioids, food-derived opioid peptides are also involved in the regulation of inflammatory processes through the opioid receptors expressed on the surface of immune cells. Furthermore, β-casomorphin was found to inhibit the proliferation of human colonic lamina propria lymphocytes (Elitsur & Luk, 1991), suggesting a role in improving local inflammation.

5 | FUNCTIONS OF FOOD-DERIVED OPIOID PEPTIDES IN PATHOLOGICAL CONDITIONS

Although food-derived opioid peptides may have physiological benefits in healthy humans, some studies implicate them in neurodevelopmental diseases and psychotic disorders in pathological conditions. For instance, elevated levels of casomorphins and gluten exorphins were observed in the urine samples of autism patients (Bojović et al., 2017), suggesting an increased gut permeability and a compromised degradation of these peptides. Indeed, autism patients are often faced with various gastrointestinal disorders, such as celiac disease, food allergies, and malabsorption (Lázaro, Pondé, & Rodrigues, 2016). Moreover, the polymorphisms on DPPIV gene and opioid excess in blood are considered to be associated with pathogenesis of autism (Cieslinska et al., 2015). These findings support the hypothesis by Dohan (1988) that, in certain genetically susceptible individuals, the incompletely digested opioid peptides, such as gliadorphins and casomorphins, might account for some of the pathogenesis of psychotic disorders, which is partly the basis for the gluten- and casein-free diets.

6 | CONCLUSIONS

In this article, we provided detailed discussion on the types, structure, and sources of opioid peptides generated by enzymatic hydrolysis of food proteins, and their functions in the central nervous and gastrointestinal systems. Food-derived opioid peptides can be beneficial to healthy human populations due to their analgesic and anxiolytic roles. However, these effects depend on peptide stability in blood and the capability of crossing the blood-brain barrier. In addition, food-derived opioid peptides may also improve diarrhea status and maintain the mucosal integrity by targeting local opioid receptors in the gastrointestinal tract. On the other hand, in certain genetically susceptible

individuals, the gastrointestinal permeability change and opioid excess may participate in the pathogenesis of some psychotic disorders. Future research is needed in characterizing the release and occurrence of the opioid peptides in food products, and the health-related molecular events they trigger across the gut-brain axis.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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