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Abstract: The centrally induced gastroprotective effect of neuropeptides has been intensively studied. Besides many similarities, however, differences can also be observed in their gastroprotective actions. The gastroprotective dose-response curve proved to be either sigmoid, or bell-shaped. Additional gastrointestinal effects of neuropeptides can contribute to their mucosal protective effect. Part of the neuropeptides induce gastroprotection by peripheral administration as well. Besides vagal nerve the sympathetic nervous system may also be involved in conveying the central effect to the periphery. Better understanding of the complex mechanism of the maintenance of gastric mucosal integrity may result in the development of new strategy to enhance gastric mucosal resistance against injury.

- Neuropeptides given centrally are potent gastroprotective agents
- Their gastroprotective dose ranges differ significantly
- Additional peripheral effects may modify their protective action
- Several peptides possess bell-shaped dose-response relationship

Brain neuropeptides in gastric mucosal protection

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Abstract

The centrally induced gastroprotective effect of neuropeptides has been intensively studied. Besides many similarities, however, differences can also be observed in their gastroprotective actions. The gastroprotective dose-response curve proved to be either sigmoid, or bell-shaped. Additional gastrointestinal effects of neuropeptides can contribute to their mucosal protective effect. Part of the neuropeptides induce gastroprotection by peripheral administration as well. Besides vagal nerve the sympathetic nervous system may also be involved in conveying the central effect to the periphery. Better understanding of the complex mechanism of the maintenance of gastric mucosal integrity may result in the development of new strategy to enhance gastric mucosal resistance against injury.

1. Introduction.

The peripheral mechanisms responsible for gastric mucosal integrity have been revealed in many aspects. Several compounds, mediators have been demonstrated to play a role in the maintenance of mucosal integrity, like bicarbonate, mucus, phospholipids, trefoil peptides, prostaglandins (PGs), sensory neuropeptides, nitric oxide (NO), hydrogen sulfide, heat shock proteins, hypoxia-inducible factor-1 or various growth factors (for reviews see e.g. [1-3,4**]). However, the role of the central nervous system (CNS) has also been raised in the regulation of gastric mucosal damage/protection. The dorsal vagal complex (DVC, including the dorsal motor nucleus of vagus (DMN), nucleus of the solitari tract (NTS) and area postrema) and the hypothalamus have prominent role in the regulation of gastrointestinal functions and well defined interconnections between the neuroendocrine hypothalamus and the central autonomic system have been described [5].

Lesion or electrical stimulation of different brain areas resulted in either development of gastric mucosal injury or stimulation of protective processes [6**]. However, most of the evidence on the involvement of CNS in regulation of gastric mucosal integrity came from pharmacological interventions. In the first experimental series mainly acid-dependent ulcer models were used, like stress-induced mucosal injury, which was inhibited by bombesin, neurotensin, β -endorphin, substance P or somatostatin injected into the cisterna magna (intracisternally, i.c.), or corticotropin-releasing factor (CRF) given into the amygdala or into the lateral brain ventricle (intracerebroventricularly, i.c.v.). Other peptides, like amylin (i.c.v.), bombesin or different opioids (injected i.c.) have been demonstrated to be effective in another acid-dependent, indomethacin-ulcer model [6**,7-8].

A new chapter was opened when thyrotropin-releasing hormone (TRH), that plays a key role in the regulation of the autonomic nervous system, injected i.c. or into the DMN in low (0.5-1.5 ng), non-secretory dose was shown to inhibit the gastric mucosal damage against ethanol injury, which is an acid-independent ulcer model and widely used for the analysis of gastroprotective action [6**,9]. This finding initiated an intensive research, and as a result several neuropeptides were shown to be gastroprotective given centrally. For example, from the calcitonin family α -CGRP (i.c.), adrenomedullin (i.c.) and amylin (i.c.v.) were highly effective against mucosal injury induced by ethanol, while calcitonin (i.c.) aggravated the ethanol-induced lesions (but reduced stress-, i.c. injected TRH analogue- or aspirin-induced mucosal damage) [6**]. From the neuropeptide Y (NPY) family peptide YY (PYY) injected i.c. at doses subthreshold to stimulate gastric acid secretion exerted also gastroprotective effect against ethanol [6**]. Furthermore, several opioid peptides (β -endorphin, [D-

Ala(2),Phe(4),Gly(5)-ol]-enkephalin (DAGO), [D-Ala(2),D-Leu(5)]-enkephalin (DADLE), [D-Pen(2),D-Pen(5)]-enkephalin (DPDPE), deltorphin II, endomorphins) (i.c.v., i.c.), as well as cholecystokinin (CCK, i.c.v.), nociceptin, nocistatin (i.c.v.), substance P (i.c.v.) and angiotensin II (i.c.v.) inhibited the formation of ethanol-induced mucosal lesions [6**,10-12, 13*,14*,15].

A special group of neuropeptides, that besides possessing a key role in regulation of food intake, are likely to play a role in gastric mucosal defense as well, for example the above mentioned PYY, CCK and amylin, as well as ghrelin (i.c.v., ischemia-reperfusion model), orexin-A (i.c., ethanol-model), leptin (i.c.v., ethanol and ischemia-reperfusion) and nesfatin-1 (i.c.v., ethanol). Moreover, TLQP-21, a vascular endothelial growth factor (VEGF)-derived peptide, which also may play a role in energy homeostasis, was also reported to exert gastroprotective effect given centrally (i.c.v., against ethanol) [6**,13*,14*,16, 17*,18].

How the centrally injected neuropeptides can induce gastric mucosal protection in the periphery, in gastric mucosa? Convincing evidence suggests the role of vagal nerve in conveying the central stimulus to the periphery. Several neuropeptides seem to induce vagal-dependent central gastroprotection, such as TRH (i.c., DMN) [6**,9], adrenomedullin (i.c.) [19], PYY (i.c.) [20], amylin (i.c.v.) [21], leptin and CCK (i.c.v.) [12], ghrelin (i.c.v.) [22], opioids, e.g. β -endorphin, deltorphin II, endomorphins (i.c.v., i.c.) [14*,23], nociceptin and nocistatin (i.c.v.) [24,25], TLQP-21 (i.c.v.) [16], substance P (i.c.v.) [10], orexin-A (i.c.) [18], angiotensin II (i.c.v.) [15] or nesfatin-1 (i.c.v.) [17*]. The peripheral mechanism of vagally mediated gastroprotective effect has been well documented by biochemical and pharmacological studies, suggesting that the activation of vagal cholinergic pathways stimulates the release of gastric mucosal PG and NO, as well as the effector function of capsaicin-sensitive afferent fibers containing calcitonin gene-related peptide (CGRP) [6**].

Though centrally injected neuropeptides induce gastroprotection mainly by common mechanisms, several differences have been demonstrated in their protective profile (Figure 1).

The aim of this review is to compare the

- gastroprotective dose range,
- dose-response relationships,
- additional gastrointestinal effects and interactions with other neuropeptides,
- central / peripheral effectiveness,
- pathways that convey the central action to the periphery of neuropeptides.

2. Differences in the gastroprotective effect of neuropeptides

2.1. The gastroprotective dose range

Neuropeptides injected i.c.v. or i.c. can be divided into different groups according to their gastroprotective dose range (Table 1). The differences in the effective dose range can be due to several reasons, such as different intrinsic activities, partial/full agonistic property, permeation of the peptides to their receptors, density of their receptors in the site of action (e.g. dorsal vagal complex) or interactions with other neuropeptides / mediators.

2.2. Dose-reponse relationships

The dose-reponse curves of neuropeptides proved to be partly sigmoid, partly bell-shaped (Figure 2). It has been recognized already 40 years ago, that increasing the dose of a peptide the effect, after reaching a plateau, can decrease, disappear or even reverse. Common characteristic of the bell-shaped (also called inverted U-shaped or hormetic) dose-response relationships is that the reduced or reversed effect may be expected typically in 10- and 100-fold of the stimulatory (inhibitory) dose-range (though the range can also be much wider) (for reviews see [26,27]).

Bell-shaped dose-reponse relationship was observed for example with RX 77368 (a stable TRH analog) [28], adrenomedullin [29], nociceptin and nocistatin [25], substance P [10] and angiotensin II [15]. In most cases the gastroprotective ranges varied between 10- and 100-fold, which is in agreement with the biphasic responses observed in other fields.

On the other hand, with other neuropeptides, such as ghrelin, opioids, amylin or nesfatin-1 the mucosal protective effect did not decline at higher doses, despite of the wide tested dose ranges [17*,21,23,30].

Interestingly, however, ghrelin or amylin has biphasic effects on other gastrointestinal functions (gastric emptying, gastric acid secretion) [31,32]. The phenomenon of bell-shaped or biphasic dose-response relationship of neuropeptides should be also considered in study designs both under experimental conditions and human trials.

Although the bell-shaped effect is rather commonly observed, the analysis of the underlying mechanism in most cases is lacking. In some cases it can be resulted from a mixed agonist/antagonist action mediated by different receptor populations. Khan et al. [33] for example reported that the biphasic effect of substance P on striatal dopamine outflow is determined by the balance between muscarinic M₁ (stimulatory) and M₂ (inhibitory) receptors.

Another possibility is that additional gastrointestinal effects, e.g. increased gastric acid secretion or altered gastric motility may counteract the mucosal protective action at higher

doses. Moreover, interactions between neuropeptides may also modify the gastroprotective effect.

2.3. Additional gastrointestinal effects and interactions of neuropeptides

TRH in higher dose range than the gastroprotective one stimulates gastric acid secretion, gastric motor activity and aggravates experimentally induced gastric mucosal lesions [35]. In contrast, nociceptin (possessing a bell-shaped dose-response curve) exerts inhibitory effect on gastric acid secretion even in 10-50 times higher dose range than the gastroprotective one (0.2-1 nmol vs. 10 nmol) and reduces gastrointestinal motor activity as well [36]. In contrast, ghrelin inhibits ischemia/reperfusion-induced mucosal lesions given i.c.v., but increases gastric acid secretion in the same dose range [22]. Moreover, ghrelin injected into the IVth ventricle or into the DVC elicited contractions of the gastric corpus via excitation of a vagal cholinergic efferent pathway [37], however, ghrelin-induced gastroprotective effect was not reduced in higher dose range. The above data suggest the lack of a definitive correlation between the declined gastroprotective effect and the increased gastric acid secretion or gastric motor activity.

In addition, numerous interactions of neuropeptides with each other or with other mediators have been described. The interactions (due for example to stimulation of the release, co-expression and co-release of neuropeptides, co-expression of the receptors) may result in augmentation or inhibition of the gastroprotective effect. Some examples: endogenous opioids are involved in the gastroprotective effect of nociceptin, nocistatin, endocannabinoids and substance P [25,38], or the endocannabinoid, 2-arachidonoylglycerol is likely to play a role in the centrally induced gastroprotective effect of angiotensin II [15]. Moreover, interactions between leptin and CCK [12] as well as RX 77368 and the PYY agonist [Pro34]PYY have been described in the ethanol ulcer model [39]. In addition, interaction between TRH and leptin in the DVC was described where TRH1 and leptin receptors are co-localized [40]. Furthermore, CCK were shown to activate orexin and neurotensin neurons [41], endomorphin-2 is co-localized with SP and CGRP in the NTS [42] and the peripherally (i.v.) given neurotensin may induce gastroprotection by activating the central endocannabinoid system [43]. Recently cannabinoids were demonstrated to affect the expression of hypothalamic neuropeptides, notably the NPY and β -endorphin systems, which may be involved in the orexigenic and gastroprotective action of cannabinoids [44].

These few, selected data suggest a complex interaction of neuropeptides with each other and with other mediators of the CNS, which may modify their gastroprotective action. Further

studies are needed to clarify the role of interaction of neuropeptides in gastric mucosal homeostasis.

2.4. Gastroprotection initiated centrally or peripherally

Some of the neuropeptides are protective only after central administration, and given peripherally either lack of effect, or even aggravation of mucosal damage can be observed. Such a phenomenon has been reported e.g. for amylin [21], adrenomedullin [19], TLQP-21 [16], or recently with angiotensin II [15,45] and substance P [10]. It might be speculated that some neuropeptides, especially in higher doses, are able to cross the brain-blood barrier by non-saturable or saturable transport mechanisms using transporters (recently reviewed by Banks [46**]) and enter the systemic circulation, where they may counteract the centrally-induced gastroprotective action via peripheral mechanisms. For example, the dose-reponse curve of angiotensin II and substance P injected i.c.v. proved to be bell-shaped (see above) and both peptides aggravated the mucosal lesions after peripheral administration, partly due to increased formation of reactive oxygen species [47,48].

On the other hand, numerous peptides exert mucosal protective action given both centrally and peripherally, like neurotensin, nesfatin-1, nociceptin, ghrelin or opioid peptides, such as DADLE, DPDPE and deltorphin II [17*,22-25,43,49], however, the central and peripheral effective dose ranges are rather different. For example, the ratios of the peripheral and central gastroprotective doses (calculated on the basis of literature data comparing either the ED₅₀ values, or the doses resulting in approximately the same gastroprotective action) are approximately 5000 for deltorphin (ethanol-injury) [23,49], 200-500 for DPDPE and neurotensin (ethanol-injury) [23,43,49], 20-80 for leptin and DADLE (ethanol-injury) [12,23,49,50] and below 10 for nesfatin-1, ghrelin, CCK-8 and nociceptin (water immersion restrain stress-, and ethanol-induced injury) [12,17*,24,25,50]. Also a peripherally injected neuropeptide may induce gastroprotective action by central mechanism, for example, as mentioned in the previous section, central cannabinoid CB₁ receptors are likely to mediate (at least partly) the gastroprotective effect of peripherally given neurotensin [43].

2.5. Factors conveying the centrally initiated effect to the periphery

As mentioned above, vagally mediated gastroprotective effect has been demonstrated for the majority of neuropeptides. However, several data suggest that besides vagal nerve other mechanisms may also play a role in conveying the centrally initiated effect to the periphery. For example both adrenergic and cholinergic systems are likely to be involved in

the gastroprotective effect of centrally injected ghrelin, since only parallel inhibition of both systems were able to abolish it [51]. Furthermore, the gastroprotective effect of angiotensin II injected into the paraventricular nucleus of the hypothalamus was not affected by subdiaphragmatic vagotomy or atropine, but was abolished by propranolol or disconnection of the nerves innervating the adrenal glands indicating the importance of the sympathetic-adrenal gland/beta-adrenoceptor pathway [52]. The gastroprotective effect of nociceptin was blocked by atropine, subdiaphragmatic vagotomy and bretylium, suggesting that both vagal cholinergic and sympathetic pathways mediate the central activity of this peptide [53]. Moreover, the protective action of neurotensin injected i.c.v. or into the n. accumbens was ameliorated by pretreatment with 6-hydroxydopamine into the mesolimbic nuclei [54]. Our recent findings also confirmed the role of sympathetic nervous system in centrally induced gastroprotection. The gastroprotective effect of opioid peptides was reduced both following bilateral cervical vagotomy and after chemical sympathectomy by 6-hydroxydopamine (i.c.v.). The later action was correlated with the reduction of the noradrenaline content in the NTS [13*].

Further studies are needed to reveal how sympathetic nervous system may mediate the centrally initiated mucosal protective effect. It should be assumed that DMN besides supplying parasympathetic pre-ganglionic fibers to the viscera contains neurons with diverse neurochemical phenotypes. For example, neurons with tyrosine hydroxylase immunoreactivity (TH-IR) have been identified in the DMN, as well as dopamine β -hydroxylase neurons were shown in the DVC (similar in number and distribution as TH-IR). It may be concluded that the TH-IR positive neurons in the DMN are capable of synthesizing norepinephrine. Moreover, these TH-IR-positive caudal DMV neurons have been demonstrated to display choline acetyltransferase activity as well [55] suggesting that activation of DVC may result in activation of both the cholinergic and adrenergic system to the peripheral targets.

3. Conclusion

Increasing number of evidence suggests the crucial role of neuropeptides in gastric mucosal integrity. However, several questions remained to be answered to elucidate their precise role in this process. For example, further studies are needed to clarify: whether changes of endogenous level of neuropeptides may result in gastroprotective (or damaging) effect; the precise anatomical background (brain areas, projections) involved in regulation of

mucosal integrity; relevance of neuropeptide-interactions in gastroprotection; how the effective gastroprotective dose range relates to other actions of the neuropeptides; and the importance of the blood-brain and brain-blood transport of neuropeptides. It may be speculated that since some peptides using transporters can enter the brain following peripheral administration (46**), they may induce gastroprotective effect by central mechanism. Vice versa, the brain-to-blood transport might result also peripheral effect following central administration of the peptides. Peripheral administration of peptides or peptide analogues which can cross the blood-brain barrier, or agents that may modify the endogenous level of gastroprotective neuropeptides might represent new therapeutic possibilities against gastric mucosal injury. Moreover, better understanding of the complex (and virtually redundant) mechanism of the maintenance of gastric mucosal integrity may serve as a basis for the development of new strategies to enhance gastric mucosal resistance against injury.

Conflicts of interest

The authors state no conflict of interest.

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** Although peptides were once assumed to not penetrate the BBB, it is now clear that they do so by both saturable and nonsaturable mechanisms. Transporters can also remove substances from the brain. The data of the review should be considered and kept in mind when the effects of neuropeptides are analysed and judged following central or peripheral administration.

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Legends

Figure 1. Similarities and differences between the centrally induced gastroprotective effect of neuropeptides.

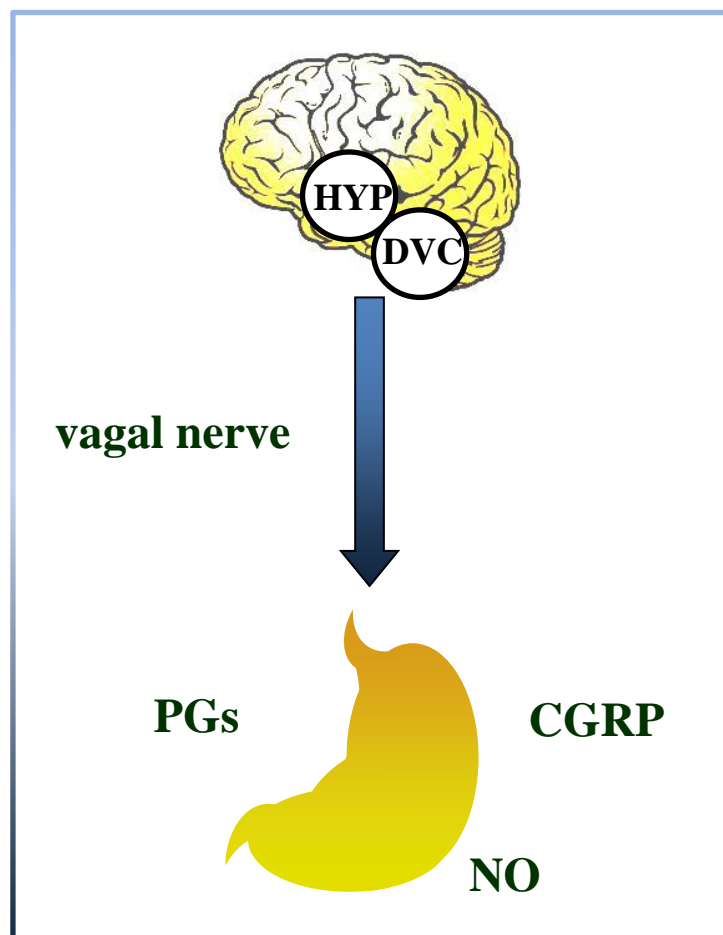
Figure 2. Dose-response relationships of various gastroprotective neuropeptides. Based on the data in references [10,15,16,17*,21-23,25,28,34].

Figure 1

CENTRAL GASTROPROTECTION INDUCED BY NEUROPEPTIDES

Similarities

Differences



- Potencies, efficacies
- Dose-response relationships
- Additional gastrointestinal effects
- Interactions with other peptides and mediators
- Central / peripheral effectiveness
- Additional pathways conveying the central action to the periphery

Figure 2

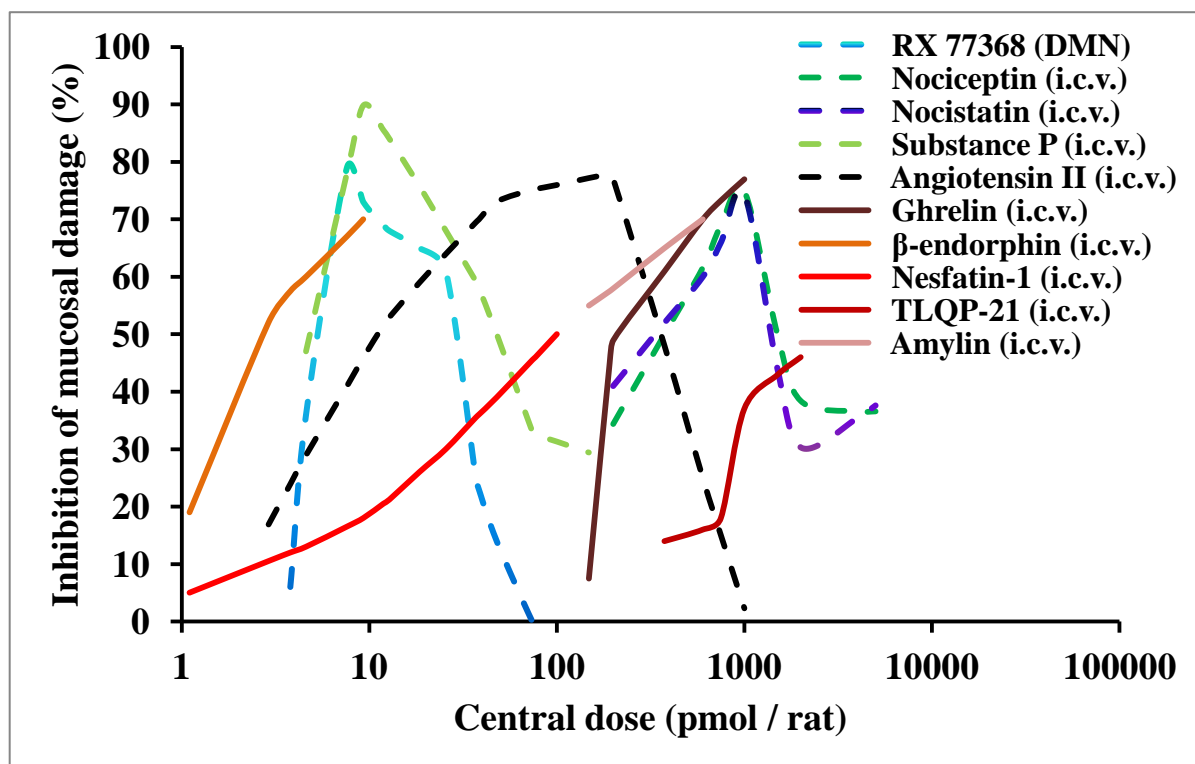


Table 1

Gastroprotective dose range	Route of administration					
	i.c.v.			i.c.		
< 1 pmol	EMs				β-endorphin	
1 - 10 pmol					β-endorphin	
10 - 100 pmol	Nesfatin-1	Leptin	Ang II		PYY	Adrenomedullin
100 - 1000 pmol	TLQP-1	N/OFQ, NST				Deltorphan II
> 1000 pmol		Ghrelin	Deltorphan II		Orexin-A	

Table 1. Groups of neuropeptides according to their gastroprotective dose range.

Abbreviations: EMs – endomorphins; SP – substance P; Ang II – angiotensin II; N/OFQ – nociception; NST – nocistatin. Based on the data in references [10,13*,15,17*,18,23].