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Review

# Regulation of feeding behavior, gastrointestinal function and fluid homeostasis by apelin

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ABSTRACT

Apelin was first identified and characterized from bovine stomach extracts as an endogenous ligand for the APJ receptor. Apelin/APJ system is abundantly present in peripheral tissues and central nervous system. Apelin plays a broad role in regulating physiological and pathological functions. Recently, many reports have showed the effects of apelin on feeding behavior, however the results are inconsistent, due to different administration routes, animal species, forms of apelin, etc. Apelin has been involved in stimulating gastric cell proliferation, cholecystokinin (CCK) secretion, histamine release, gastric acid and bicarbonate secretion, and regulation of gastrointestinal motility. In addition, apelin produced regulatory effects on drinking behavior, diuresis, arginine vasopressin (AVP) release and glucocorticoids secretion. This article reviews the role of apelin on feeding behavior, gastrointestinal function and fluid homeostasis.



**Contents**



## 1. Introduction

In 1998, Tatemoto's group purified a peptide from ovine stomach extracts by measuring extracellular acidification in a Chinese hamster ovary (CHO) cell line expressing the human G protein-coupled receptor APJ. The peptide was identified as the endogenous ligand of the human orphan APJ, so it was called 'apelin', for APJ endogenous ligand [48]. The human apelin gene, localized on chromosome Xq25-q26.1, encodes a 77 amino acid prepropeptide precursor (preproapelin) [18]. The human, bovine and rat preproapelin peptides have a fully conserved sequence in the last 23 C-terminal amino acids, between Trp-55 to Phe-77 [37]. The preproapelin undergoes maturation generating several active peptide fragments: apelin (42–77), named apelin-36, apelin

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**Table 1**
The amino acid sequence and molecular weight (MW) of human preproapelin and apelin fragments [7,15,48].

| Peptide name | Amino acid sequence | MW (kDa) |
|---|---|---|
| Preproapelin | MNLRCVQALLLLWLSLTAVCGGSLMPLPDGNGLEDGNVRHLVQPRGSRNGPGPWQGGRRKFRRQRPRLSHKGPMPF | 9.810 |
| Apelin-36 | LVQPRGSRNGPGPWQGGRRKFRRQRPRLSHKGPMPF | 4.195 |
| Apelin-31 | RGPRSGPGWQGGRRKFRRQRPRLSHKGPMPF | 4.138 |
| Apelin-28 | RSGPGWQGGRRKFRRQRPRLSHKGPMPF | 3.301 |
| Apelin-19 | RRKFRRQRPRLSHKGPMPF | 2.450 |
| Apelin-17 | KFRRQRPRLSHKGPMPF | 2.138 |
| Apelin-16 | FRRQRPRLSHKGPMPF | 2.010 |
| Apelin-15 | RRQRPRLSHKGPMPF | 1.863 |
| Apelin-13 | QRPRLSHKGPMPF | 1.550 |
| Apelin-12 | RPRLSHKGPMPF | 1.422 |

(47–77), named apelin-31, apelin (50–77), named apelin-28, apelin (59–77), apelin-19, apelin (61–77), named apelin-17, apelin (62–77), named apelin-16, apelin (63–77), named apelin-15, apelin (65–77), named apelin-13 and apelin (66–77), named apelin-12 [7,15,48] (as shown in Table 1). Apelin-17 and apelin-13 strongly suppress forskolin-stimulated cAMP production in CHO cells expressing the human APJ [8,24] and display the highest activity on extracellular acidification rate [48]. Of note, apelin-13 is the most potent activator of cells lines expressing APJ [8,15,48]. The APJ, encoded by a gene mapped to chromosome 11, possesses a 40–50% sequence homology and shares closest identity to the angiotensin II type 1 receptor; however, it does not bind angiotensin II [26,32]. The apelin and APJ are widely distributed in central nervous system (CNS) and peripheral tissue in both human and rodents [16]. In the CNS, apelin and APJ mRNAs have been found in brain, cerebellum, pituitary and spinal cord [12,30,37]. In the periphery, they have been detected in the lung, heart, kidney, stomach, intestine, adrenal gland, etc. [12,18,30]. Many physiological roles for the apelin/APJ system have emerged, including cardiovascular function [7,19], immune response [2,11], adipoinsular axis, etc. [1,53]. This review outlines the role of apelin on feeding behavior, gastrointestinal function and fluid homeostasis.

## 2. Feeding behavior

### 2.1. Inhibition on feeding behavior

The distribution of apelin/APJ system in hypothalamus suggests a role on apelin in energy homeostasis. Many reports have showed the regulation of apelin on feeding behavior. However, the results were not consistent, as shown in Table 2. Intracerebroventricular (i.c.v.) injection of 1 and 3 nmol of apelin-13 resulted in a reduction in food intake in both fed and 24-h fasted Wistar rats. However, intravenous (i.v.) injection of 10 nmol of apelin-13 did not cause any change in food intake in either fed or fasted rats [42]. Interestingly, i.c.v. injection of 10 nmol apelin-12 10 min prior to lights out, led to significant reductions in food intake 2–4 h after injection, suggesting that apelin-12 also exerts a delayed inhibitory effect on nocturnal feeding [35]. Clarke et al. found that 2 μg apelin-13, administered (i.c.v.) prior to lights out, decreased food in diet-induced obese (DIO) rats on the control diet, but had no effect in DIO rats on the high-fat diet [3]. The similar inhibitory effect of apelin-13 was also found in Kunming mice. I.c.v. injection of 3 μg apelin-13 induced a significant food intake in freely feeding mice and 24-h fasted mice during the dark period, but during light period, apelin-13 (1–3 μg, i.c.v.) had no influence on food intake in freely feeding mice. The inhibition of apelin-13 on food intake seems to be mediated by APJ and corticotrophin-releasing factor (CRF) receptor, but not arginine vasopressin (AVP) receptor [22].

### 2.2. Stimulation on feeding behavior

On the other hand, the stimulatory effect of apelin on feeding behavior was also indicated in the recent reports (Table 2). In fasted rats, the third cerebra ventricle (3 V) injection of 30 nmol pyroglutamylated apelin-13 ([pGlu]-apelin-13) significantly increased food intake at 2–4 h, but had no significant effect at any other time point or on cumulative 24-h food intake. However, [pGlu]-apelin-13 at doses of 3, 10 and 30 nmol had no effect on food intake when administered (3 V) to fed rats [44]. I.c.v. administration of 10 nmol apelin-12 to satiated rats also stimulated feeding during day time [35]. In addition, Higuchi et al. found that intraperitoneal (i.p.)

**Table 2**
Overview of the experimental conditions and the effects of apelin on food intake in recent literature.

| Ref. | Administration route | Species/strain | Form of apelin | Dose | Food deprivation | Time of administration | Effect |
|---|---|---|---|---|---|---|---|
| [42] | ICV, acute | Rats, Wistar | Apelin-13 | 1 or 3 nmol | No or 24 h | 2 h after light onset | ↓ |
| | IV, acute | Rats, Wistar | Apelin-13 | 10 nmol | No or 24 h | 2 h after light onset | N |
| [35] | ICV, acute | Rats, SD | Apelin-12 | 10 nmol | No | Before dark onset | ↓ |
| | ICV, acute | Rats, SD | Apelin-12 | 10 nmol | No | After light onset | ↑ |
| [3] | ICV, acute | Rats, DIO-C | Apelin-13 | 2 μg | No | 15–30 min before dark onset | ↓ |
| | ICV, acute | Rats, DIO-HF | Apelin-13 | 2 μg | No | 15–30 min before dark onset | N |
| [22] | ICV, acute | Mice, Kunming | Apelin-13 | 3 μg | No or 24 h | Before dark onset | ↓ |
| | ICV, acute | Mice, Kunming | Apelin-13 | 0.3–3 μg | No | After light onset | N |
| [44] | 3V, acute | Rats, Wistar | [pGlu]-apelin-13 | 3–30 nmol | No | 2 h after light onset | N |
| | 3V, acute | Rats, Wastar | [pGlu]-apelin-13 | 30 nmol | Over night | 2 h after light onset | ↑ |
| [10] | IP, choric | Mice, C57BL/6 | Aplein-13 | 0.1 μmol/kg | No | 3:00 p.m. | N |
| [49] | 3V, chronic | Mice, C57BL/6 | Apelin-13 | 1 μg/day | No | Not specified | ↑ |
| [50] | ICV, acute | Goldfish | Apelin-13 | 1 or 10 ng/g | No | During light phase | ↑ |
| | IP, acute | Goldfish | Apelin-13 | 50 or 100 ng/g | No | During light phase | ↑ |

ICV, intracerebroventricular; IP, intraperitoneal; 3V, the third cerebral ventricle; SD, Sprague–Dawley; DIO-C, diet-induced obese rats on the control diet; DIO-HF, diet-induced obese rats on the high-fat diet; ↓, suppression food intake; ↑, stimulation food intake; N, no effect.