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Review

Is GPR39 the natural receptor of obestatin?

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ABSTRACT

GPR39, an orphan receptor belonging to the family of G protein-coupled receptors, was originally reported to be the receptor of obestatin. However recently, numerous reports have questioned this conclusion. In mammals, GPR39 was reported to be involved in the regulation of gastrointestinal and the metabolic functions. In this article, a latest and brief review on the receptor family, structure, distribution and physiological functions of GPR39 has been reported.

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1. Introduction

The G protein-coupled receptor 39 (GPR39) is an orphan member of a family including the receptors for ghrelin and motilin [30]. GPR39 shows a high degree of constitutive signaling through the serum response element (SRE) pathway [20]. In 2005, GPR39 was reported to be the receptor for a peptide fragment from the ghrelin precursor named obestatin, which was reported to be a gut hormone having the opposite effect on food intake and GI-tract function to ghrelin [52]. Thereafter, the GPR39 signaling was activated by zinc ions (Zn^{2+}) through the G α-PLC pathway [48]. However, Chartrel et al. [8] suggested that obestatin did not activate GPR39; therefore, the natural ligand for GPR39 is uncertain so far. In this article, we summarized the receptor family, structure, distribution and physiological functions of GPR39.

2. Receptor family of GPR39

In 1996, the growth hormone secretagogue receptor (GHS-R) gene was cloned and shown to encode a unique G protein-

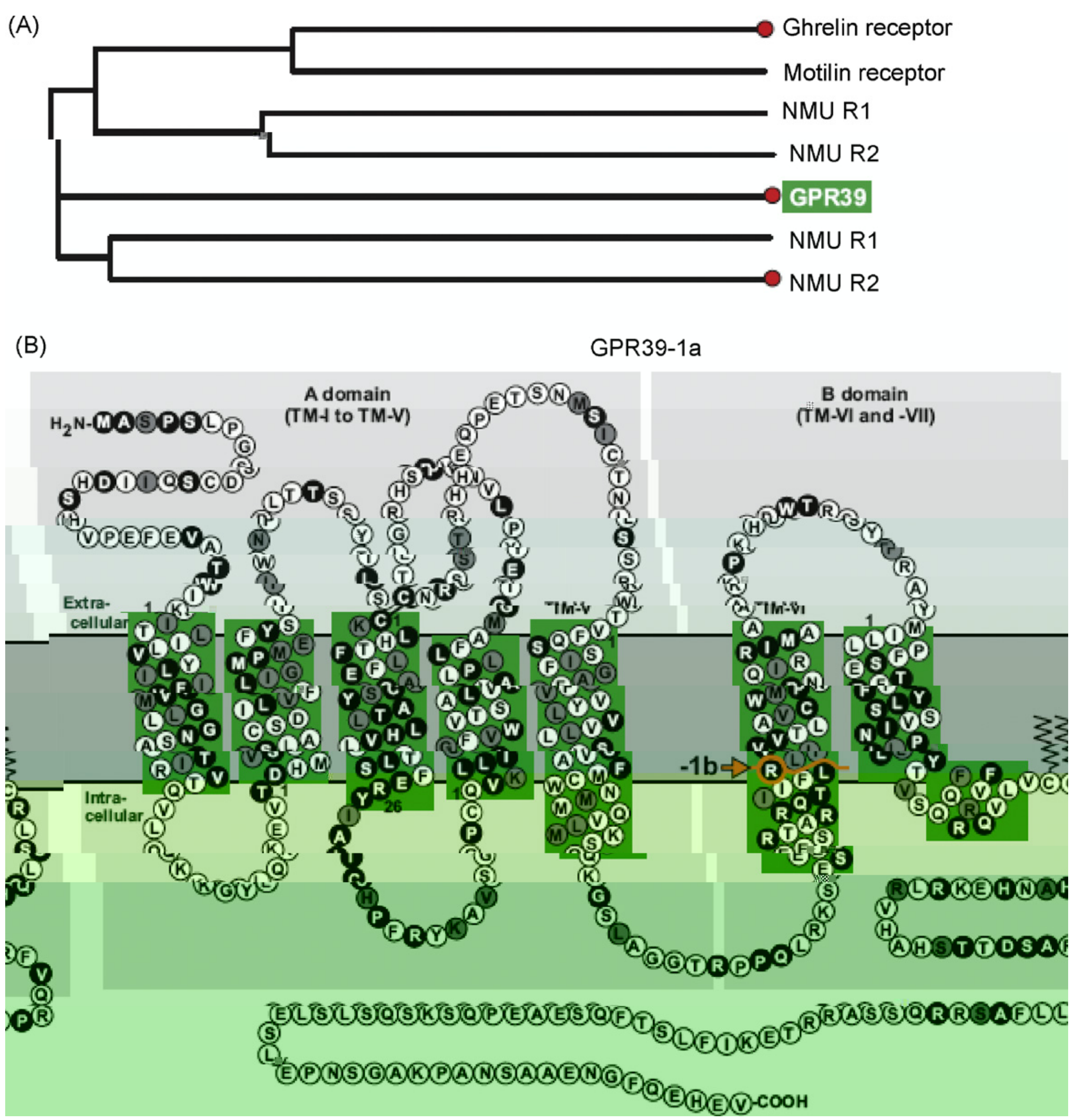

Fig. 1 – The receptor family of GPR39. (A) Schematic phylogenic tree of the receptor family of GPR39. The constitutively active receptors are highlighted with red color. (B) A model of human GPR39. GPR39-1a is the full length 7-transmenbrane (TM) receptor, and GPR39-1b is a truncated form of GPR39-1a lacking after 5-TM [12,41]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

c led ece with a ded ced ein e ence ha wa 96% iden ical in h man and a [22]. Beca e f he hy i gical im ance f he GHS-R, a ea ch f family membe wa hen ini ia ed and i m lec la e l n wa in e iga ed. McKee e al. iginally indica ed ha GPR38 and GPR39 ha ed a igni can amin acid e ence iden ical wi h he GHS-R, ne medin U ece and he ne en in ece (Fig. 1A). Fl e cence *in situ* hyb idi a- n dem n a ed ha GPR38 and GPR39 cali ed a e a a e ch m me and we e di inc f m he gene enc ding he GHS-R and NT-R y e 1 [30].

GPR38 wa enc ded by a ingle gene e e ed in he hy id gland, mach, and b ne ma w, and i i n w kn wn be he ece f m ilin, which mainly eg la e ga in e inal (GI) c n ac n and g m ili y [13]. GPR39 wa e e ed in he b ain and he e i he al i e [30]. The GHS-R gene wa la e indica ed be he ece f he GI- ac h m ne gh elin in l ed in a la ge a ay f

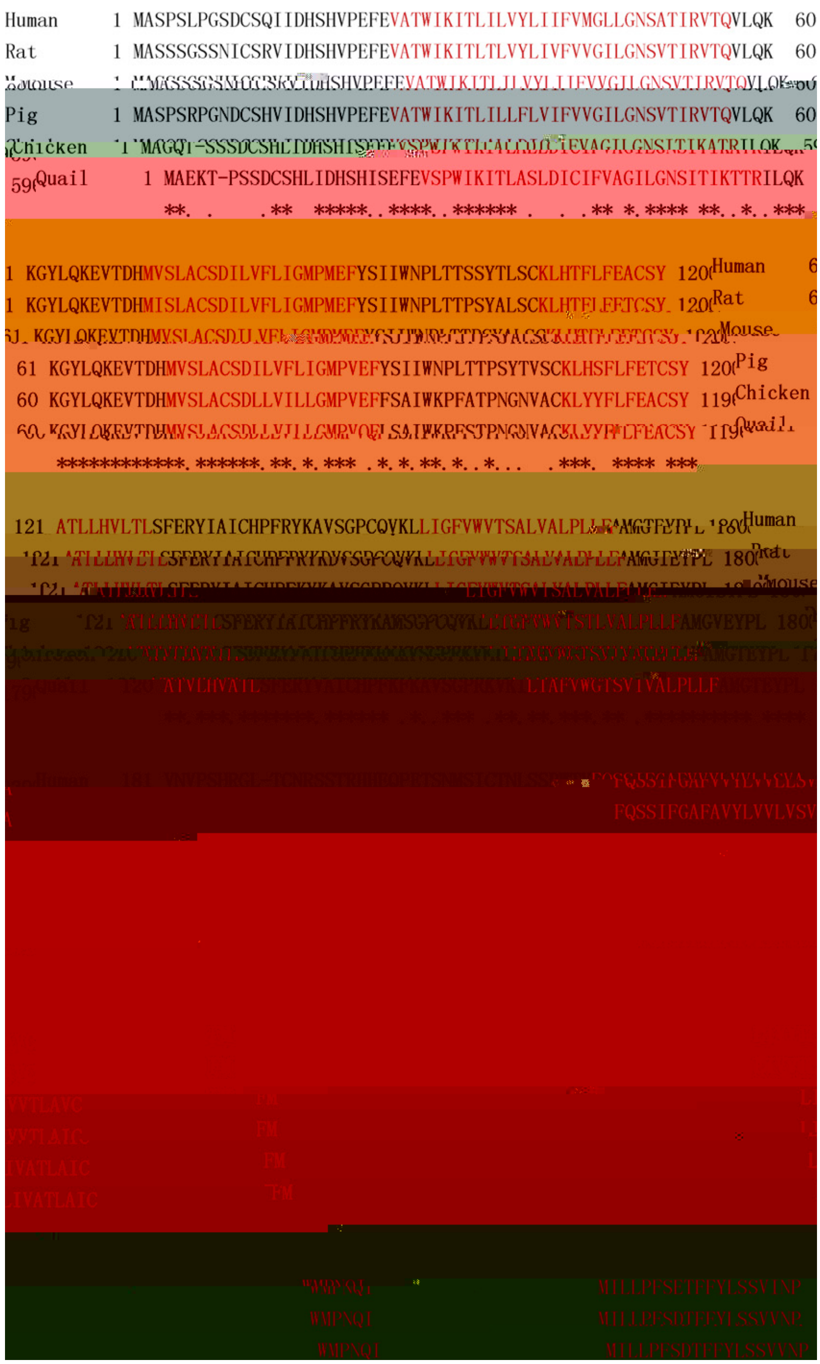

Fig. 2 – Alignment of amino acid sequences of human, mouse, rat, chicken, quail and pig GPR39. Transmembrane regions were represented as red letters; the gene sequences are quoted from GenBank accession (nos. NM001508, NM001114392, ENSRNOG00000021586, NM001080105, EF375709, and EU669821). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

physiological functions including the regulation of food intake, body weight, GI motility and hypothalamic and hypophyseal hormone secretion [18,27,33,49]. Other members of the GPR39 receptor family are neuromedin U receptors and neurotensin receptors. Neuromedin U and neurotensin both have been implicated in the control of food intake and GI functions [21,54].

3. Structure and distribution of GPR39

3.1. *Structure of the GPR39 receptor*

The GRP39 receptor belongs to the class of rhodopsin-like receptor family including GHS-R and motilin receptor (GPR38) [20,30]. The amino acid sequences of GPR39 in human, rat, mouse, quail, chicken and pig are shown in Fig. 2.

The molecular weight of human GPR39 is 52 kDa [14]. The human GPR39 gene consists of two exons separated by a very large intron of approximately 200 kb [36]. PCR analysis verified the notion that GPR39 was expressed by two splice variants, namely GPR39-1a, corresponding to the full length 7-transmenbrane (TM) receptor, and GPR39-1b, corresponding to a truncated form of GPR39-1a lacking after 5-TM (Fig. 1B) [12]. Yamamoto et al. [46,47] reported the amino acid sequences and gene structures of chicken and quail GPR39. Chicken and quail GPR39 both encode a 462-amino acid protein, with high sequence homology to human, rat and mouse GPR39. The quail GPR39 cDNA consisted of 354 bp of 5′-UTR, 1484 bp of 3′-UTR and 1389 bp of coding region [47]. The chicken GPR39 gene is composed of two exons separated by an intron, HNF-1, GC box and CCAAT box, but no canonical TATA box was found in the chicken GPR39 gene [46]. Recently, we determined the pig GPR39 cDNA encoding a 465-amino acid protein (Fig. 2).120

f nc_i nal analy_i_ f _he GPR39 m _e egi n iden_i ed _ha_ HNF-1α, HNF-4α, and SP1 e e in l ed in _he c n_ l f GPR39 e e__i n [12].

In mice, GPR39 mRNA e e__i n a_ de_ec_ed in _e _ m-amygdala, a ie_al cell_, en_e cy_e_, ne n_ and anc ea_ [31], in e i he al gan_ _ ch a_ _he d den m and kidney b _m _ in _he i_ i_a y and hy _halam _ by Q-PCR [19] and in a i _ b ain egi n_ e ce _ _he hy _halam _ by *in situ* hyb idi a_i n [24]. By RT-PCR and imm n cy chemi_ y, Igle_ia_ e_ al. [23] e _ed _ha_ GPR39 mRNA a_ e e__ed in m ine ca di my cy_e_ c l_ ed *in vitro*.

In bi d_, Yamam _ e_ al. e _ed a de_ail di_ ib _i n f GPR39 mRNA in chicken_, he e a ide ange f _i__ e_ di_ ib _i n a_ b_e ed i_h _he highe_ le el in _he d den m, and m de a_e le el_ in _he li e , kidney, _ mach and id c_. The e e__i n le el_ e e l in _he b ain i_ i_a y, _hym _, b _a f fab ici _, b ne ma , a y and _e_i_. E e__i n le el_ f GPR39 mRNA e e al_ mea_ ed by Q-PCR in dige_i e and e d c_i e _i__ e_ in 1-yea ld

GPR39 [52]. M echa e al. [31] and Zhang e al. [50] gge ed ha be a in a a h m ne ca able f binding GPR39 eg la e he f nc n f di e e ga in e inal and adi e i e . F he die indica ed ha be a in a in l ed in inhibi ing hi and an ie [37], im ing mem [6], affec ing cell life a n [5,53], c n lling id h me a i [38] and inc ea ing he ec e n f anc ea ic j ice en me [25]

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