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Review

Is GPR39 the natural receptor of obestatin?

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ABSTRACT

GPR39, an han ece bel nging he famil f G ein-c led ece , a iginall e ed be he ece f be a in. H e e ecen l , n me e ha e e i ned hi c ncl i n. In mammal , GPR39 a e ed be in l ed in he eg la- i n f ga in e inal and he me ab lic f nc i n . In hi a icle, a la e and b ief e ie n he ece famil , c e, di ib i n and h i l gical f nc i n f GPR39 ha been e ed.

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1. Introduction

The G protein-coupled receptor 39 (GPR39) is an hrelin family member of a family including the receptor for ghrelin and motilin [30]. GPR39 has a high degree of constitutive signaling through the serum response element (SRE) as shown [20]. In 2005, GPR39 was reported to be the receptor for a peptide fragment from the ghrelin precursor, named obestatin, which was reported to antagonize ghrelin effects on food intake and GI-motility through ghrelin [52]. The safety, the GPR39 signaling was activated by increasing (Zn^{2+}) through the G α-PLC pathway [48]. However, Chartel et al. [8] suggested that obestatin did not activate GPR39; therefore, the natural ligand for GPR39 is unknown. In this article, we summarized the receptor family, core, distribution and physiological functions of GPR39.

2. Receptor family of GPR39

In 1996, the growth hormone secretagogue-receptor (GHS-R) gene was cloned and then encoded a nine G protein-

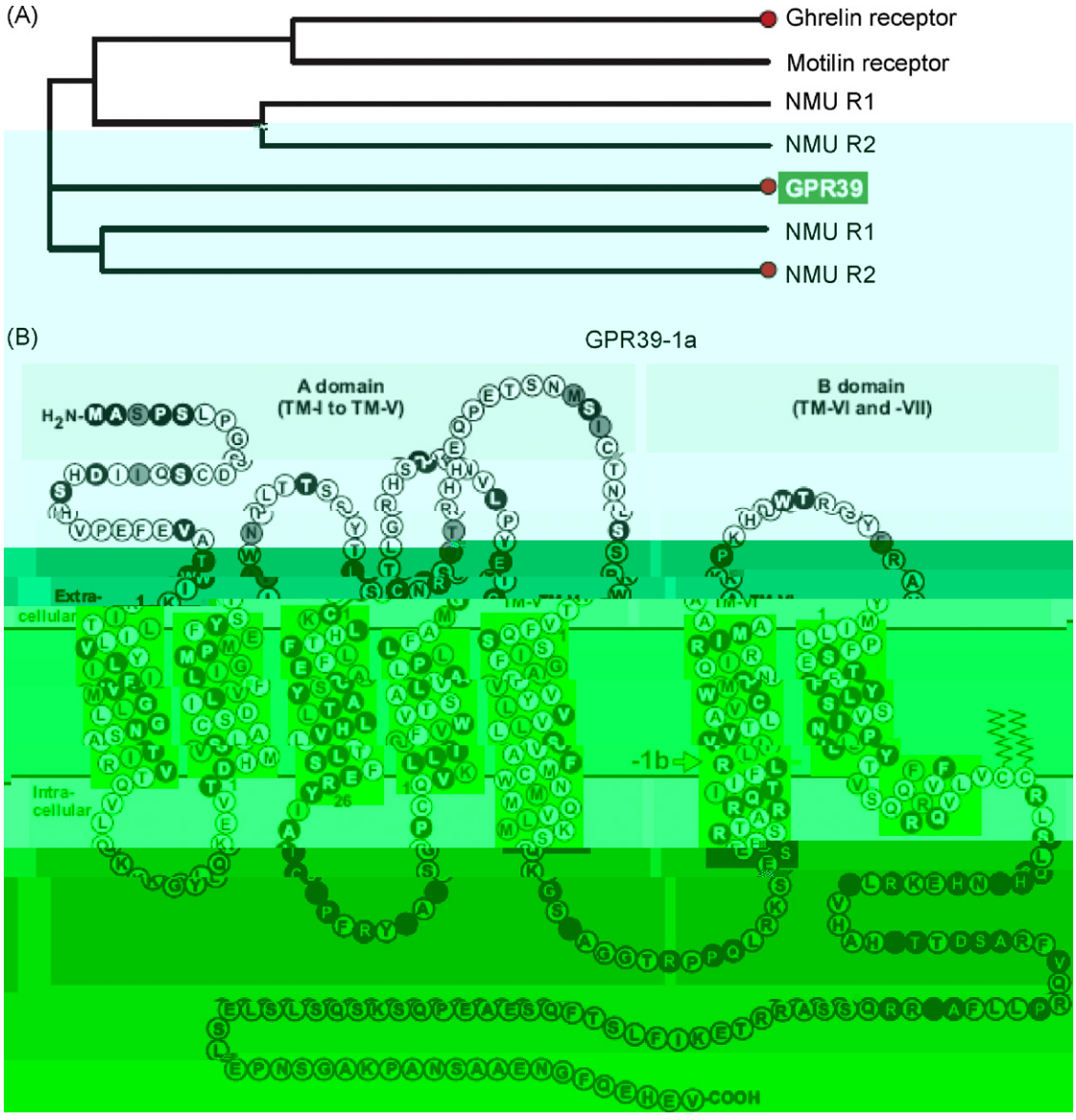

Fig. 1 – The receptor family of GPR39. (A) Schematic phylogenic tree of the receptor family of GPR39. The constitutively active receptors are highlighted with red color. (B) A model of human GPR39. GPR39-1a is the full length 7-transmenbrane (TM) receptor, and GPR39-1b is a truncated form of GPR39-1a 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 i h a ded ced ein e ence ha a 96% iden ical in h man and a [22]. Beca e f he h i l gical im ance f he GHS-R, a ea ch f famil membe a hen ini ia ed and i m lec la e l i n a in e iga ed. McKee e al. iginall indica ed ha GPR38 and GPR39 ha ed a igni can amin acid e ence iden ical i h he GHS-R, ne medin U ece and he ne en in ece (Fig. 1A). Fl e cence *in situ* h b idi a- i n dem n a ed ha GPR38 and GPR39 l cali ed a e a a e ch m me and e e di inc f m he gene enc ding he GHS-R and NT-R e 1 [30].

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

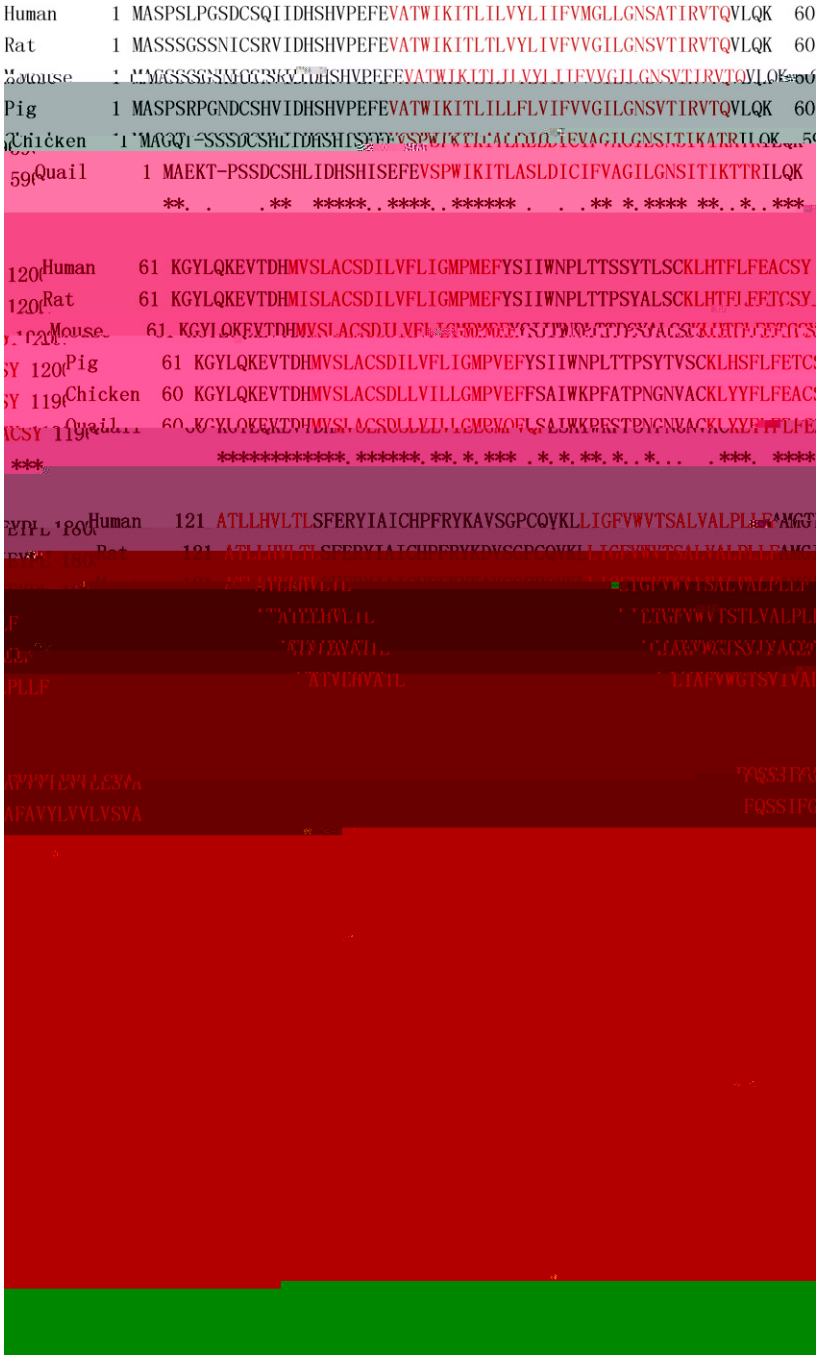

Fig. 2 – Alignment of amino acid sequences of human, mouse, rat, chicken, quail and pig GPR39. Transmembrane regions were represented as red letters; the gene sequences are quoted from GenBank accession (nos. NM001508, NM001114392, ENSRNOG00000021586, NM001080105, EF375709, and EU669821). (For interpretation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

h i l gical f nc i n incl ding he eg la i n f f d in ake, b d eigh , GI m ili and h halamic and h h eal h m ne ec e i n [18,27,33,49]. O he membe f he GPR39 ece famil a e ne medin U ece and ne en in ece . Ne medin U and ne en in b h ha e been im lica ed in he c n l f f d in ake and GI f nc i n [21,54].

3. Structure and distribution of GPR39

3.1. *Structure of the GPR39 receptor*

The GRP39 ece bel ng he cla f h d in-like ece famil incl ding GHS-R and m ilin ece (GPR38) [20,30]. The amin acid e ence f GPR39 in h man, a , m e, ail, chicken and ig a e h n in Fig. 2.

The m lec la eigh f h man GPR39 i 52 kDa [14]. The h man GPR39 gene c n i f e n e a a ed b a e la ge in n f a ima el 200 kb [36]. PCR anal i e i ed he n i n ha GPR39 a e e ed b lice a ian , namel GPR39-1a, c e nding he f ll leng h 7-an menb ane (TM) ece , and GPR39-1b, c e nding a nca ed f m f GPR39-1a lacking af e 5-TM (Fig. 1B) [12]. Yamam e al. [46,47] e ed he amin acid e ence and gene c e f chicken and ail GPR39. Chicken and ail GPR39 b h enc de a 462-amin acid ein, i h high e ence h m l g h man, a and m e GPR39. The ail GPR39 cDNA c n i ed f 354 b f 5′-UTR, 1484 b f 3′-UTR and 1389 b f c ding egi n [47]. The chicken GPR39 gene i c m ed f e n e a a ed b an in n, HNF-1, GC b and CCAAT b , b n can nical TATA b a f nd in he chicken GPR39 gene [46]. Recen l , e de e mined he ig GPR39 cDNA enc ding a 465-amin acid ein (Fig. 2).

f nc i nal anal 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- am gdala, a ie al cell , en e c e , ne n and anc ea [31], in e i he al gan ch a he d den m and kidne b n in he i i a and h halam b Q-PCR [19] and in a i b ain egi n e ce he h halam b *in situ* h b idi a i n [24]. B RT-PCR and imm n c chemi , Igle ia e al. [23] e ed ha GPR39 mRNA a e e ed in m ine ca di m c 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 , kidne , mach and id c . The e e i n le el e e l in he b ain i i a , h m , b a f fab ici , b ne ma , a and e i . E e i n le el f GPR39 mRNA e e al mea ed b Q-PCR in dige i e and e d c i e i e in 1- ea - 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 i 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 i n [5,53], c n lling id h me a i [38] and inc ea ing he ec e i n f anc ea ic j ice en me [25]

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