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Review

Is GPR39 the natural receptor of obestatin?

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ABSTRACT

GPR39, an han ece bel nging he family 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_ ned hi_ c ncl _ n. In mammal_, GPR39 a_ e ed be in l ed in he eg la- n f ga_ in e_inal and he me ab lic f nc n_. In hi_ a icle, a la e_ and b ief e ie n he ece family, c e, di_ ib n and h _ gical f nc n_ f GPR39 ha_ been e ed.

Contents

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1. Introduction

The G protein-coupled receptor 39 (GPR39) is an orphan 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) activity [20]. In 2005, GPR39 was deorphanized by the receptor for a 28-residue fragment from the ghrelin precursor, named obestatin, which was found to bind and inhibit ghrelin effects on food intake and GI-tract function [52]. The early GPR39 signaling was activated by increased (Zn^{2+}) through the Gq α-PLC pathway [48]. However, Chanoine et al. [8] suggested that obestatin did not activate GPR39; the effect, the natural ligand for GPR39 is unclear, and is a matter of debate. 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 found to encode a unique G protein-

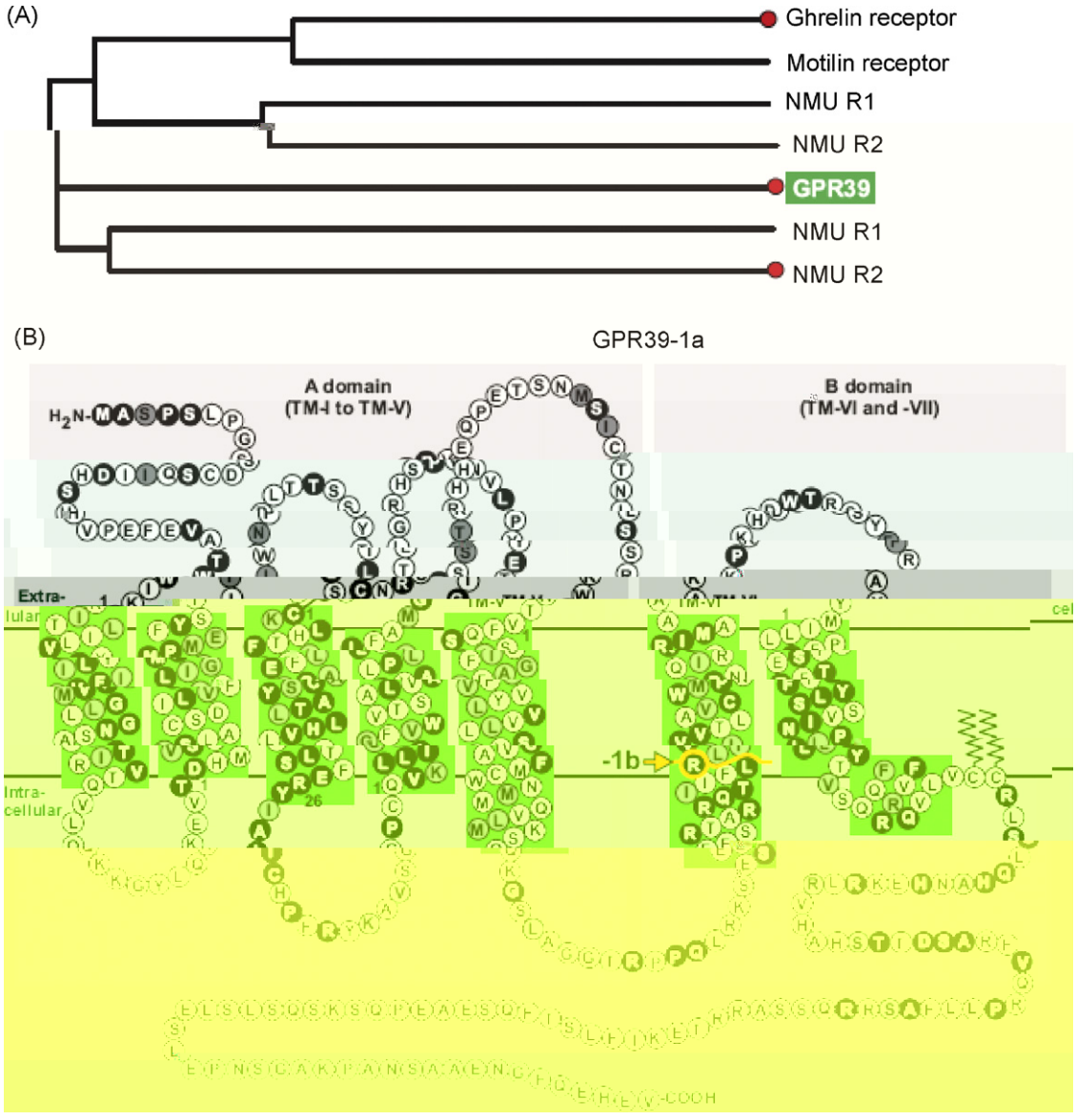

Fig. 1 – The receptor family of GPR39. (A) Schematic phylogenic tree of the receptor family of GPR39. The constitutively active receptors are highlighted with red color. (B) A model of human GPR39. GPR39-1a is the full length 7-transmenbrane (TM) receptor, and GPR39-1b is a truncated form of GPR39-1a 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 i h a ded ced ein e ence ha a 96% iden ical in h man and a [22]. Beca e f he hy i l gical im ance f he GHS-R, a ea ch f family membe a hen ini ia ed and i m lec la e l n a 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 i 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 e e di inc f m he gene enc ding he GHS-R and NT-R e 1 [30].

GPR38 a enc ded by a ingle gene e e ed in he hy id gland, mach, and b ne ma , and i i m kn n be he ece f m ilin, hich mainly eg la e ga in e inal (GI) c n ac n and g m ili y [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 ay f

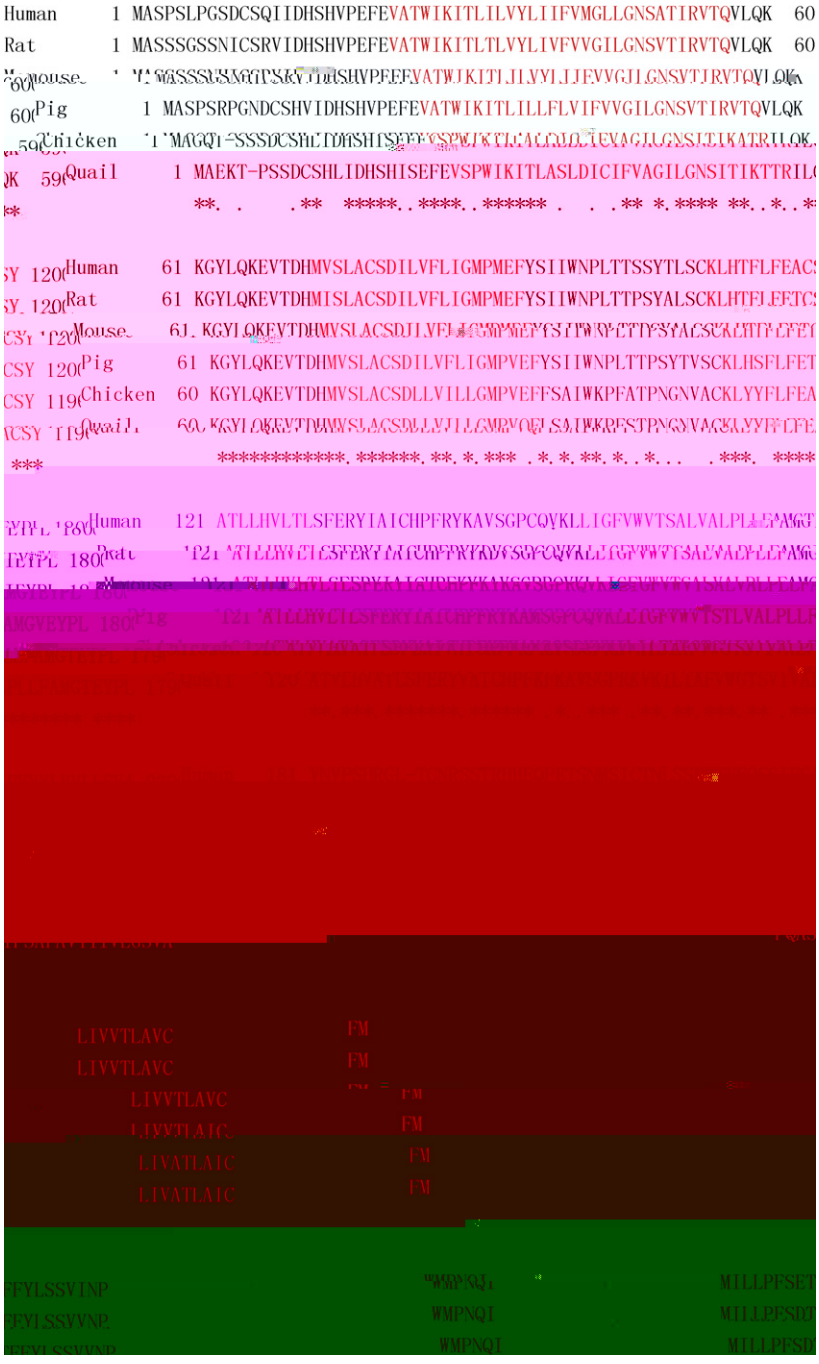

Fig. 2 – Alignment of amino acid sequences of human, mouse, rat, chicken, quail and pig GPR39. Transmembrane regions were represented as red letters; the gene sequences are quoted from GenBank accession (nos. NM001508, NM001114392, ENSRNOG00000021586, NM001080105, EF375709, and EU669821). (For interpretation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

hy_i* l* gical f nc_i* n_ incl ding _he eg la_i* n * f f** d in_ake, b* dy \eigh_, GI m* _ili_y and hy * _halamic and hy * hy_eal h* m* ne_ec e_i* n [18,27,33,49]. O_he membe _ * f _he GPR39 ece _* family 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 _* family 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 by a e y la ge in_ * n * f a * ima_ely 200 kb [36]. PCR analy_i_ e i ed _he m* _i* n _ha_ GPR39 \a_ e e__ed by _* _ lice a ian__, namely 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* gy _* 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 by an in_ * n, HNF-1, GC b* and CCAAT b* , b _ m* can* nical TATA b* \a_ f* nd in _he chicken GPR39 gene [46]. Recen_ly, \e de_e mined _he ig GPR39 cDNA enc* ding a 465-amin* acid * _ein (Fig. 2).

f nc_ 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_ n [12].

In mice, GPR39 mRNA e e_ n a_ de_ec_ed in _e m-am gdala, 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 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_ n [24]. B RT-PCR and imm n cy chemi_ , Igle_ia_ e_ al. [23] e _ed _ha_ GPR39 mRNA a_ e e_ ed in m ine ca di m 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 , kidne , _ mach and id c_. The e e_ n le el_ e e i in _he b ain i_ i_a , _hm _, b _a f fab ici _, b ne ma , a and _e_i_. E e_ 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 n f di e ga in e inal and adi e i e. F he die indica ed ha be a in a 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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The a _h* _g a_ef lly ackn* wledge D . H. Kaiya (De a _men_ *f Bi* chemi_ y, Na_i* nal Ca di* a_c la Cen_e Re_ea ch In_i _e, O_aka, Ja an) f* hi_ al able c* mmen_ _* n _hi_ a e . Thank_ a e al_* e _ended _* Mi_ _ Clai e (a _ den_ _ dying ab* ad f* m R* anda) f* he al able g idance and _ gge_i* n* f _hi_ a e .

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