



Minireview

What is the general action of ghrelin for vertebrates? – Comparisons of ghrelin's effects across vertebrates

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ABSTRACT

Ten years and more passed since ghrelin was discovered. Various physiological actions of ghrelin have been documented in both mammalian and nonmammalian vertebrates. Do these actions have any commonality? In this review, we focused on several effects of ghrelin, and compared the effect across vertebrates. We would like to discuss possible general function of ghrelin in vertebrates.

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1. Introduction

Ghrelin passed 13-years from its discovery [47]. At the time, ghrelin secreted by the stomach was caught with surprise because it is a digestive organ, and mRNA of the ghrelin receptor (GHS-R1a) had been detected predominantly in the brain and pituitary. Ghrelin is a peptide identified as an endogenous ligand to an orphan GPCR (GHS-R1a) for artificial compounds, growth hormone secretagogues (GHS), stimulates growth hormone (GH) release *in vivo* and *in vitro*. It showed the novel pathway for GH release as the only peripheral gut hormone to stimulate GH release: an indirect pathway through the vagal nerve afferent as well as the direct action to the pituitary gland through circulation [13,14].

Now it has been well recognized that ghrelin is present in non-mammalian vertebrates [40,41]. Comparing the structure of ghrelin and its receptors in all vertebrate species, it is possible to examine the molecular evolution of the ghrelin system. Further, various physiological functions have been documented. However, genetically modified animals, mainly used rodents, of the ghrelin-gene (*ghrelin*) or the ghrelin receptor-gene (*ghsr*) have been established, and we came to know the fundamental role of ghrelin in animals [51,53,88]. In this review, we would like to discuss on what is the essential role of ghrelin in vertebrates while narrowing down a focus to some actions, and inspecting the effect with each animal class.

2. Comparisons of representative ghrelin's effects across vertebrates

We picked up representative physiological functions of ghrelin in Fig. 1, and would like to add comments every each item below.

2.1. GH-releasing activity

It is well documented that ghrelin acutely stimulates GH secretion from the pituitary *in vivo* and *in vitro*. At first, Kojima et al. [47] demonstrated that ghrelin specifically stimulated GH release *in vivo* and *in vitro* in rats. Thereafter the GH-releasing property of ghrelin was reported in human [95]. At present, the GH-releasing activity has been confirmed in various mammalian species such as cattle [24,96], goats [26], pigs [25,75,79], dogs [8] and sheep [22,28,94].

In nonmammalian vertebrates, studies were also directed to the demonstration of GH-releasing activity of ghrelin since its history of the discovery [40]. However, because of the difficulties in the methodology of measuring pituitary hormones, reports were come from limited animals. Ghrelin stimulates GH release in chickens *in vivo* and *in vitro* [1,7,34], bullfrog *in vitro* [36], tilapia *in vivo* and *in vitro* [15,38,39,73], rainbow trout *in vivo* and *in vitro* [37], goldfish *in vivo* and *in vitro* [38,39,73], orange-spotted grouper *in vitro* [72], sea bream *in vitro* [11], channel catfish *in vivo* [43] and hybrid striped bass *in vivo* and *in vitro* [71]. Artificial compounds such as GHRP-6 and hexarelin are also effective, probably through GHS-R1a, in a few fish species such as tilapia [82], sea bream [11] and rainbow trout [83]. However, Xiao et al. [107] have reported the absence of GH-releasing activity by GHSs in immature

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	Mammals	Aves	Amphibian	Fish
				
GH release	Stimulate /No effect	Stimulate	Stimulate	Stimulate /No effect?
Corticosteroids release	Stimulate /No effect	Stimulate	Stimulate	Stimulate
Feeding (ICV)	Stimulate /No effect	Inhibit	-	Stimulate /Inhibit
Feeding (IP, IV)	Stimulate /No effect	Inhibit /No effect	-	Stimulate /No effect
Plasma level during fasting	Increase (Fast response)	Increase (Fast response)	Increase (Slow response)	Increase (Slow response)
GI contraction	Contraction (In vivo)	Contraction (In vitro)	-	No effect (In vitro)
Drinking	Inhibit (IV, ICV)	Inhibit (ICV)	No effect (ICV)	Inhibit (IV, ICV)

Fig. 1. Comparisons of ghrelin's effects across vertebrates. Representative physiological effects of ghrelin and the results are summarized.

grass carp (*Ctenopharyngodon idellus*) *in vivo* and *in vitro*, but we cannot say that ghrelin is ineffective in this species at present.

2.2. Corticosterone-releasing activity

The fact that ghrelin increases plasma cortisol level was reported in human study by Takaya et al. [95]. In mammals, several lines of evidence indicate that ghrelin stimulates corticosteroid release only in limited animals: humans [4,61,81], pigs [79], cows [29], mice [5] and rats [58,85,105]. On the other hand, ghrelin does not induce cortisol release in dogs [8] and sheep [28]. Animals that respond to ghrelin also increase ACTH level, but animals that do not respond to ghrelin do not change the level, suggesting the mediation of the hypothalamo–pituitary–adrenal (HPA) axis. In addition, ghrelin does not directly stimulate corticosteroid release and its steroidogenic route although ghrelin and ghrelin receptor are present in the adrenal gland [2,6,76]. On the other hand, there is a report that prolonged exposure of adrenocortical cells to ghrelin directly stimulates corticosterone secretion [76].

In nonmammalian vertebrates, a few papers have been reported about corticosterone-releasing activity. In fish, Breves et al. [9] reported approximately 2-times increased plasma cortisol level in summer flounder after intraperitoneal (IP) injection of ghrelin. Furthermore, we have observed a tendency to increase plasma corticosterone levels in bullfrog when 2 nmol ghrelin injected intravenously (IV) (A. Koda, H. Kaiya, K. Yamamoto, S. Kikuyama, unpublished observation). In chickens, IV or intracerebroventricular (ICV) injection of ghrelin increases plasma corticosterone levels in a dose-dependent manner [10,34,64,78]. The effect is clearer than the GH-releasing activity [34], but we do not know what is the major role of increased corticosterone after ghrelin treatment.

2.3. Feeding regulation and associated plasma ghrelin level

Precedent studies had showed that central or peripheral injection of GHS increases food intake and body weight in rats [52,97], suggesting some effects of the endogenous ligand, ghrelin. Expectedly ghrelin stimulates feeding in rats and humans, which was attracted attention as ghrelin is the only peripheral hormone that promotes food intake [103,104]. On the other hand, in mice and pigs, it has been reported that ghrelin does not affect on food

intake although plasma ghrelin level has increased by the ghrelin administration [21,79,99]. Also, in sheep, IV, ICV or intramuscular injection of ghrelin failed to stimulate voluntary food intake [28,49] although Harrison et al. [22] reported the stimulatory effect. These results indicate that ghrelin does not necessarily increase feeding behavior in mammals. Meanwhile, increase in plasma ghrelin level is observed in the negative energy state such as fasting in rats, cattle and humans [3,26,59,98,102]. In sheep that ghrelin fails to stimulate food intake, a transient ghrelin surge in plasma before meal disappeared in sheep fed *ad libitum* [86], and a cholinergic pathway is involved in this phenomena [27,87]. Taken together, it does not seem to necessarily assure that plasma ghrelin levels and feeding behavior are correlative in mammals.

Variations have also been found in nonmammals such as fish and birds. In goldfish, ghrelin acutely increases food intake when injected centrally or peripherally [55,56,100,101]. Meanwhile ghrelin levels in serum begin to increase 3 days after fasting and retained high level until 7 days of fasting [101]. The increased response of ghrelin level seems to be slow against an acute effect on food intake. Riley et al. [74] showed an increase in food intake and body weight by a chronic administration of ghrelin in tilapia. Fox et al. [16] reported short-, medium- and long-term changes in plasma ghrelin levels in tilapia, and showed significant increases 2 and 4 weeks of fasting but not for 8 days of fasting. In rainbow trout, Shepherd et al. [83] showed a stimulation of food intake, whereas Jönsson et al. [32] observed no effect after IP ghrelin injection in juvenile fish. Jönsson et al. [33] demonstrated that ICV injection of ghrelin inhibits food intake in juvenile fish by mediating the CRF system. They also observed an inhibition of feeding for 14-days treatment of ghrelin. Plasma levels of ghrelin do not show any postprandial changes [32], but Pankhurst et al. [67] saw an increase in plasma ghrelin level 24 h after a single feeding. The stimulant of ghrelin secretion in rainbow trout is not sure at present. In birds, ICV injected ghrelin always inhibits food intake in chickens and quail [19,31,77,84,91,93]. However, there are cases where different actions are seen when ghrelin injected IV in chickens: broiler shows inhibitory action [10,20,64], and layers does not show any effect [42]. In Japanese quail, stimulatory or inhibitory effect is seen when high and low dose of ghrelin injected IV, respectively [84]. Buysse et al. [10] indicated a different mechanism

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