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Influence of estrogen and the endocrine disruptor on the calcitonin functions in teleosts

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Abstract: In this review, we discuss the function of calcitonin (CT) during teleost reproduction and the influence of estrogen and bisphenol-A (BPA) on CT functions. CT acts as a hypocalcemic hormone in mammals. However, the hypocalcemic effect of CT remains unclear in teleosts. The effect of CT on the plasma calcium level varies among fish species and experimental conditions. On the other hand, CT has significant functions in terms of teleost reproduction. Plasma CT levels in some teleosts are higher in females than in males. Additionally, a correlation between plasma CT concentration and the gonadal somatic index is observed in female teleosts. In the reproductive period, estrogen (17 β -estradiol), a sex steroid, induces the synthesis of vitellogenin in the liver and promotes calcium resorption from the scales by activating osteoclasts. Vitellogenin possesses a calcium-binding property and is incorporated into oocytes through the vitellogenin receptor. The estrogen receptor is present in the ultimobranchial gland (UBG), which is the source of CT in non-mammals. The estrogen receptor is expressed in the UBG, and specific estrogen binding is detected in the UBG. In addition, estrogen induces CT secretion from the UBG. Furthermore, using the scale *in vitro* assay system, we found that osteoclastic activity accelerated by the estrogen was suppressed by CT. These findings imply that CT protects the scales from excess degradation of calcium at the time of teleost vitellogenesis. Additionally, we introduce the function of an endocrine disruptor such as BPA in calcium metabolism. The actions of BPA in calcium homeostasis are different from those of 17 β -estradiol. BPA suppressed both osteoclastic and osteoblastic activities and decreased both the plasma CT and calcium levels. Collectively, these issues lead to the conclusion that CT has significant function(s) during specific stages, such as reproduction, and that BPA acts differently from estrogen and disrupts the CT functions.

Keywords: Calcitonin, Estrogen, Bisphenol-A, Reproduction, Endocrine disruption, Teleosts

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Introduction

Calcitonin (CT) is a 32-amino acid peptide hormone that is conserved in the gnathostomes (Sekiguchi, 2018). CT is synthesized in the thyroid C-cells and the ultimobranchial gland (UBG) by mammalian and non-mammalian species, respectively (Azria, 1989). In mammals, CT acts as a hypocalcemic hormone that can mineralize bones by suppressing osteoclastic

activity. Therefore, it has been utilized as a drug to cure human osteoporosis (Ukon *et al.*, 2019).

CT function in fish remains ambiguous, although fish CT has a strong hypocalcemic activity in mammals (Azria, 1989). The effect of CT on the blood calcium level is contradictory and varies among fish species and experimental conditions (Dacke, 1979; Wendelaar Bonga and Pang, 1991; Srivastav *et al.*, 1998; Lafont *et al.*,

2011). There are some reports that CT performs a hypocalcemic action in the teleost (Mukherjee *et al.*, 2004; Lafont *et al.*, 2011). For instance, the treatment of salmon CT inhibited whole-body calcium uptake in *Channa punctatus* and *Cyprinus carpio* (Mukherjee *et al.*, 2004). CT decreased whole-body calcium levels in zebrafish *via* the downregulation of epithelial calcium channel expression (Lafont *et al.*, 2011). In contrast, CT induced hypercalcemia in the grey mullet, rainbow trout, and brown trout (Fouchereau-Peron *et al.*, 1987; Oughterson *et al.*, 1995). In some cases, the treatment of fish CT does not exhibit any remarkable effect on calcium homeostasis (Hirano *et al.*, 1981; Srivastav *et al.*, 1998). Chan (1972) suggested that the absence of a hypocalcemic effect of CT in fish seems to be due to their high levels of circulating CT; the fish may be saturated with circulating CT and not be capable of an apparent response to exogenous CT.

On the other hand, the correlation between CT and reproduction has been reported. The UBGs of some teleosts are known to be maximally active during reproductive period (Oguri, 1973; Yamane and Yamada, 1977; Sasayama *et al.*, 2001; Verma and Alim, 2015). In addition, the plasma CT level in the sockeye salmon (*Oncorhynchus nerka*) was higher in females than in males during the spawning season (Watts *et al.*, 1975). Similar results have been reported in the freshwater teleost, *Mastacembelus armatus* (Verma and Alim, 2015). Furthermore, the increase in plasma CT has been observed before ovulation in eels, *Anguilla japonica* (Yamauchi *et al.*, 1978), salmonid fishes such as rainbow trout, *Salmo gairdneri* (Björnsson *et al.*, 1986), and brown trout, *Salmo trutta* (Norberg *et al.*, 1989). This implies that CT is associated with sexual maturation, especially in female teleosts. In this review, we discuss the physiological significance of CT during teleost reproduction and the influence of the endocrine disruptor on calcium metabolism in teleosts.

Estrogen directly acts on the UBG and promotes CT secretion:

Estrogen is a sex steroid hormone involved in the female reproduction of gnathostomes. It is also associated with bone metabolism and participates in osteoblastic differentiation in mammals (Komm *et al.*, 1988; Eriksen *et al.*, 1988; Okazaki *et al.*, 2002; Noirrit-Esclassan *et al.*, 2021). Therefore, the relationship between estrogen and blood calcium homeostasis has been investigated in teleosts. Three subtypes of estrogen receptors (ERs) were expressed in the goldfish UBG (Suzuki *et al.*, 2004). The cytosol extract of UBG bound to 17 β -estradiol (E₂) (Suzuki *et al.*, 2004). Furthermore, CT secretion was increased by E₂ in rainbow trout, goldfish, and zig-zag eels (Björnsson *et al.*, 1989; Suzuki *et al.*, 2004; Verma and Alim, 2015). A positive correlation between the plasma CT level and the gonad somatic index was detected in female goldfish (Suzuki *et al.*, 2004). In female goldfish, plasma calcium concentration is also correlated with plasma CT (Suzuki *et al.*, 2004). These findings strongly suggest that CT is related to sexual maturation and calcium homeostasis during reproduction in female teleosts.

Bisphenol-A inhibits CT secretion and disrupts calcium homeostasis:

Bisphenol-A, 4,4'-isopropylidenediphenol (BPA), is a major component of epoxy resins that are used in protective coatings. This compound possesses estrogenic properties and acts through the estrogen receptor, which is categorized as an endocrine disruptor (Safe *et al.*, 2001). The disturbance of fish reproduction by BPA has been reported (Gould *et al.*, 1998; Luconi *et al.*, 2001). BPA also disturbs the bone metabolism in fish (Suzuki *et al.*, 2003; Thent *et al.*, 2018). BPA treatment decreased both plasma CT and calcium concentrations in goldfish (Suzuki *et al.*, 2003). The actions of BPA in calcium metabolism were different from those of E₂ because both plasma CT and calcium increased with E₂ treatment (Björnsson *et al.*, 1989; Suzuki *et al.*, 2004). Therefore, we suggest that BPA disrupts calcium homeostasis through a different pathway from that of E₂ in teleost scales.

The relationship between CT and E₂ in the scale osteoclasts: CT suppresses enhanced osteoclastic activities by E₂:

Although most teleosts have acellular bones, which are characterized by the absence of osteoblasts and osteoclasts (Weiss and Watabe, 1979; Ekanayake and Hall, 1988), the teleost scale is comprised of the osteoclasts and osteoblasts that are similar to those found in avian and mammalian bone (Yamada, 1961, 1971; Bereiter-Hahn and Zylberberg, 1993). In addition, the osteoblast and osteoclast of teleost scales are regulated by hypercalcemic and hypocalcemic hormones (Suzuki *et al.*, 2016). Therefore, teleost scale is a more functional internal calcium reservoir than vertebral bone during periods of increased calcium demand, including sexual maturation (Berg, 1968; Mugiya and Watabe, 1977; Bereiter-Hahn and Zylberberg, 1993).

An assay system using the teleost scale is available to analyze the effect of hormones on osteoblastic and osteoclastic activity (Suzuki *et al.*, 2000; Suzuki and Hattori, 2002). Since tartrate-resistant acid phosphatase (TRAP) and alkaline phosphatase (ALP) are involved in the osteoclastic and osteoblastic functions, the activity of these enzymes has been used as a marker of osteoclastic and osteoblastic activity (TRAP: Vaes, 1988; ALP: Dimai *et al.*, 1998; Okazaki *et al.*, 2002). E₂ and CT are crucial hormones for analyzing the relationship between reproduction and calcium homeostasis. The correlation between CT and E₂ in goldfish (a freshwater teleost) and nibbler fish (a seawater teleost) was evaluated in their cultured scales (Suzuki *et al.*, 2000). In goldfish scales, CT inhibited TRAP activity, whereas E₂ activated TRAP activity. Moreover, the stimulation of osteoclastic activity by E₂ was inhibited by CT treatment in a dose-dependent manner. Similar results were obtained with the scales of female nibbler fish. However, CT treatment did not alter ALP activities in goldfish or nibbler fish scales (Suzuki *et al.*, 2000; Kase *et al.*, 2017). Taken together, these findings indicate that CT has the

potential to protect scales from excess degradation of calcium by E₂ during teleost reproduction.

BPA suppresses scale osteoclastic and osteoblastic activities:

The direct effects of BPA on osteoclasts and osteoblasts were examined using a culture system of goldfish scales. BPA (10⁻⁵ M) significantly suppressed both TRAP and ALP activities in the scales (Suzuki and Hattori, 2003). These data were reproduced in an *in vivo* experiment (Suzuki and Hattori, 2003). Expression analysis using Reverse Transcription-PCR indicated the suppression of insulin-like growth factor (IGF)-1 mRNA, which is related to osteoblastic growth and differentiation (Hock *et al.*, 1988; Billiard *et al.*, 2001). In contrast, E₂ stimulated both TRAP and ALP activities and did not change IGF-1 mRNA expression. These findings indicate that BPA has a different action from E₂ in the bone metabolism as well as in the plasma calcium and CT level regulation.

CT directly functions on ovary in teleosts:

The direct function of CT in the teleost ovary has been reported (Paul *et al.*, 2008; Das *et al.*, 2014). In common carp, *Cyprinus carpio*, treatment with salmon CT induced E₂ secretion *in vivo* and *in vitro*. A receptor binding assay using radiolabeled CT revealed that CT specifically binds to the cytosol of the oocyte (Paul *et al.*, 2008). Additionally, CT stimulated oocyte maturation in the follicle culture in an estuarine flathead gray mullet, *Mugil cephalus* L (Das *et al.*, 2014). These studies suggest that CT directly acts on the ovary and plays a role in oocyte maturation in teleosts.

Physiological significance of the CT function:

During reproduction in female teleosts, both E₂ and CT regulate calcium homeostasis. Figure 1 summarizes a successive hormonal event in teleost vitellogenesis. Firstly, the plasma E₂ level increases remarkably to induce vitellogenin synthesis in the liver and promotes calcium

resorption from the scales by activating the osteoclasts (Persson *et al.*, 1995; Suzuki *et al.*, 2000). Secondly, vitellogenin, which is a major component of egg protein and a calcium-binding protein (Tinsley, 1985; Kwon *et al.*, 1993), is translocated into the oocyte through the vitellogenin receptor (Norberg *et al.*, 1989). Thereafter, CT secretion was induced by E₂ via the ERs in the UBG (Suzuki *et al.*, 2004). This increased CT suppresses the osteoclastic action enhanced by E₂ in the scale (Suzuki *et al.*, 2000). Subsequently, plasma calcium levels decreased. Taken together, this indicates that the plasma calcium concentration is regulated by the interaction between CT and E₂ and that CT certainly performs a significant action during this period. In addition, CT stimulates E₂ release and oocyte maturation in the ovary.

Fig. 1: Physiological significance of calcitonin (CT) during reproduction. Estrogen, especially 17 β -estradiol (E₂), acts on the liver and promotes vitellogenin (VTG) synthesis. In addition, E₂ acts on the UBG and scale. The scale is an internal calcium (Ca) reservoir in teleosts. The plasma Ca was regulated by the interaction between CT and E₂ in the scale. Furthermore, CT acts directly on the ovary and plays some roles that have yet to be identified.

On the other hand, an endocrine disruptor such as BPA suppresses CT secretion and inhibits scale osteoclastic and osteoblastic activities. Suppression of these scale bone cells induces a decline in plasma calcium levels (Fig. 2). These results indicate that the effect of BPA is different from that of E₂. Therefore, the detailed

mechanism of BPA in calcium homeostasis needs to be studied.

Fig. 2: Influence of bisphenol-A (BPA) on calcium (Ca) homeostasis. The effect of BPA is different from that of E₂ and is a disruption of Ca homeostasis. Although BPA induces vitellogenin (VTG) synthesis in the liver, it suppresses CT secretion and inhibits the activities of osteoclasts and osteoblasts in scales. As a result of suppression of the scale osteoclasts and osteoblasts, plasma Ca level seems to be decreased. Further study is required to elucidate the mechanism of BPA influence on Ca metabolism.

Conclusion

From the results of these studies, it can be concluded that--(i) During reproduction, plasma calcium is regulated by the interaction between CT and E₂. In contrast, the actions of BPA in calcium metabolism were different from those of estrogen. BPA disturbs calcium homeostasis, (ii) In teleosts, CT is not functional under normal conditions, whereas CT has significant function(s) during reproduction.

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