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# Adiponectin: A Novel Hormone in Birds

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## ABSTRACT

Adiponectin is an adipokine hormone that influences several metabolic functions including glucose utilization, lipogenesis, energy homeostasis and immunity by signaling through two distinct receptors, AdipoR1 and AdipoR2. AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver. AdipoR1 and AdipoR2 genes are ubiquitously expressed in chicken tissues and that their expression is altered by feed deprivation in the anterior pituitary gland and adipose tissue. Adiponectin and its receptors expressed in chicken testis. Suggesting that adiponectin either produced locally or from other sources can influence testicular function. These findings indicate that sexual maturation is associated with the up-regulation of adiponectin receptor gene expression in the chicken testis. Also, adiponectin, AdipoR1 and AdipoR2 mRNAs are expressed in chicken theca and granulose cells from preovulatory follicles. Adiponectin is highly expressed in theca cells as compared to granulose cells and could be involved in the development of chicken preovulatory follicle. Differences in the adiponectin expression level observed in different tissues suggest that the adiponectin gene has broad functions in the metabolism process. In order to reveal the function and mechanism of action of adiponectin in life, more considerable and penetrating work should be pursued.

**Key words:** Adiponectin, AdipoR1, AdipoR2

## INTRODUCTION

Adiponectin, which was also termed as adipocyte complement-related protein (ACRP30), adipose most abundant gene transcript 1 (apM1), gelatin-binding protein 28 (GBP28) and AdipoQ (Scherer *et al*., 1995; Hu *et al*., 1996; Maeda *et al*., 1996; Nakano *et al*., 1996) is a 30 kDa adipokine hormone secreted primarily from adipose tissue in several mammalian species. Adiponectin exerts its action by binding to two specific receptors, AdipoR1 and AdipoR2. AdipoR1 and AdipoR2 genes are likely to mediate the physiological effects of adiponectin. In addition, chicken AdipoR1 and/or AdipoR2 may also regulate de novo expression of the adiponectin gene in tissues in an autocrine and/or paracrine regulatory pathway (Maddineni *et al*., 2005). For example, adiponectin and its receptors expressed in chicken testis, it is possible that adiponectin influences metabolism in peritubular cells and interstitial cells and may affect spermatogenesis. Ramachandran *et al*. (2007) have cloned the chicken AdipoR1 and AdipoR2 cDNA and found that both genes are ubiquitously expressed in multiple tissues of the chicken. In addition, they found that both AdipoR1 and AdipoR2 gene expression in the chicken anterior pituitary gland and adipose tissue are significantly altered by feed deprivation. Maddineni *et al.* (2005) reported adiponectin mRNA expression in chicken various tissues was quantitated using real-time quantitative PCR and found to be the highest in adipose tissue, followed by liver, anterior pituitary, diencephalon, kidney and skeletal muscle. Liver is the primary site of lipid biosynthesis (Leveille *et al.*, 1975) in avian species, unlike mammals, in which fat synthesis occurs in white adipose tissue. Adiponectin expressed in the chicken liver may play a regulatory role in lipid metabolism, glucose utilization and gluconeogenesis. Maddineni *et al.* (2005) found that the chicken pituitary gland and diencephalon expressed greater amounts of adiponectin mRNA next to adipose tissue and liver. Phenotypic identities of diencephalonic neurons or anterior pituitary gland cells that express adiponectin gene in the chicken are not known at this time. In the anterior pituitary gland, adiponectin gene may possibly be coexpressed in GH-secreting cells, based on the finding that plasma GH concentrations are inversely related to adiponectin concentrations in mice (Berryman *et al.*, 2004) and in humans (Lam *et al.*, 2004). In addition, folliculo-stellate cells in the anterior pituitary gland may possibly express adiponectin mRNA because these cell types have been found to express several other cytokines (Inoue *et al.*, 1999). In the chicken diencephalon, adiponectin gene is possibly expressed in hypothalamic neurons that control secretion of several hormones from the pituitary gland, including GH. It is also likely that adiponectin gene expression in the chicken diencephalon may affect energy homeostasis based on the report that intracerebroventricular administration of adiponectin in mice decreased body weight by stimulating energy expenditure (Qi *et al.*, 2004). Also, Maddineni *et al.* (2005) reported food deprivation resulted in a significant decline in adiponectin mRNA quantity in adipose tissue, liver and anterior pituitary gland, indicating that adiponectin gene expression is closely linked to energy balance in these tissues. Acute food deprivation decreased adiponectin gene expression in the white adipose tissue of rats (Zhang *et al.*, 2002). Similarly, subcutaneous and epididymal adipose tissue adiponectin mRNA quantity was decreased in response to fasting (Bertile and Raclot, 2004). Fasting decreases gene expression of other adipocyte proteins such as leptin (Amstalden *et al.*, 2000), resistin (Morash *et al.*, 2004) and adiponutrin (Baulande *et al.*, 2001) in the adipose tissue. Anterior pituitary gland expression of other adipose-specific cytokines was found to be affected by food restriction (Wiesner *et al.*, 2004). It is likely that fasting would stimulate conservation of energy and therefore attempt to down-regulate expression of adiponectin, a hormone known to promote energy expenditure. It is also possible that a decrease in adiponectin gene expression need not necessarily mean a decrease in adiponectin protein concentration in either the adipose tissue or blood circulation.

## DISCOVERY

Much attention has been paid to the adiponectin gene, since it was first isolated and cloned from mouse fatty tissue by Scherer *et al.* (1995). The adiponectin gene coding regions in many species have been cloned and published, including human (NC-000003), rat (NM-144744), mouse (NM-009605), pig (AY627882), dog (AB110099), cow (NM-174742), chicken (AY786316) and duck (DQ452618). Mammalian adiponectin genes, which contain three exons and two introns, are highly conserved between species (Hu *et al.*, 1996; Maeda *et al.*, 1996; Jacobi *et al.*, 2004). The distinction between poultry and mammalian adiponectin is obvious: chicken and duck adiponectin only contain two exons and one intron (Yuan *et al.*, 2006) whereas, those of mammals have three exons and two introns); the homology between these two species is 86% and they only have 66% homology with mammals.

## STRUCTURE

Adiponectin is a 244 amino acid long polypeptide. There are four distinct regions of adiponectin. The first is a short signal sequence that targets the hormone for secretion outside the cell; next is a short region that varies between species; the third is a 65-amino acid region with similarity to collagenous proteins; the last is a globular domain. Figure 1 had showed adiponectin structure. Maddineni *et al.* (2005) cloned the full-length chicken adiponectin cDNA. The chicken adiponectin cDNA is 65-68% homologous to pig, human, mouse, or dog adiponectin cDNA, whereas the deduced protein sequences was 51-61% similar to mammalian adiponectin (Table 1). The deduced amino acid sequence of chicken adiponectin cDNA revealed a series of 22 Gly-X-Y repeat at the N-terminal end, in which X and Y denote any amino acids. Distal to the Gly-X-Y repeats, the amino acid sequences were found to show a slightly higher degree of homology (72.1%) to the globular domain of human adiponectin protein (Tsao *et al.*, 2003). Multiple cysteine residues found in the deduced chicken adiponectin protein may aid in the formation of multimeric forms of adiponectin, as reported with mammalian adiponectin (Tsao *et al.*, 2003).

## RECEPTORS : TISSUE DISTRIBUTION AND MRNA EXPRESSION

Adiponectin exerts its action by binding to two specific receptors, AdipoR1 and AdipoR2. Both AdipoR1 and AdipoR2 are seven transmembrane receptors that are structurally and functionally distinct from G-protein-coupled receptors (Yamauchi *et al.*, 2003b) AdipoR1 is abundantly expressed

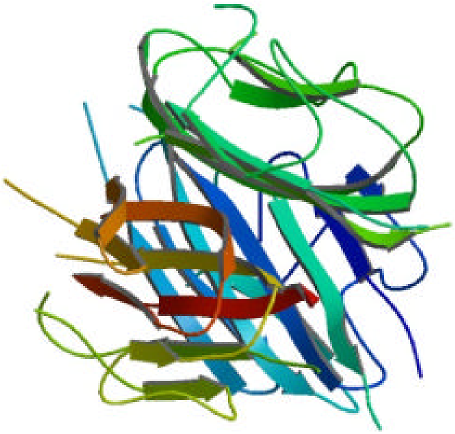

Fig. 1: Adiponectin structures

Table 1: Similarity of chicken adiponectin to mammalian adiponectin

| Species | GenBank accession No. | Nucleotide identity | Amino acid identity |
|---|---|---|---|
| | | (%) | (%) |
| Dog | AB110099 | 68 | 58 |
| Cow | NM174742 | 67 | 61 |
| Human | NM004797 | 66 | 57 |
| Pig | AY135647 | 66 | 51 |
| Mouse | MMU37222 | 65 | 60 |

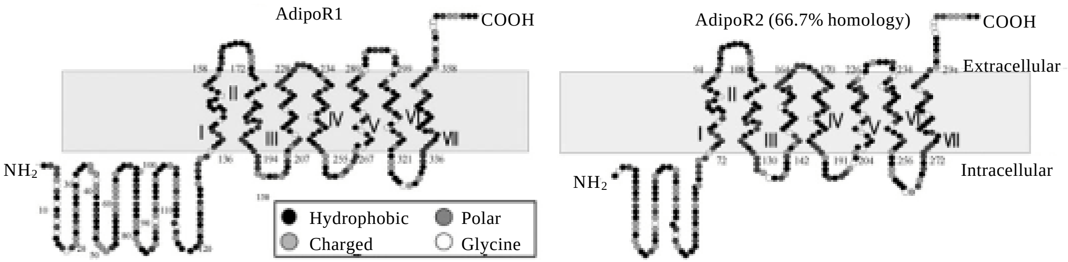

Fig. 2: Proposed structure of adiponectin receptors and their expression in various tissues. cDNA encoding adiponectin receptors (AdipoR1 and R2) were isolated. AdipoR1 was ubiquitously expressed and most abundantly expressed in skeletal muscle, whereas AdipoR2 was most abundantly expressed in mouse liver (Yamauchi *et al.*, 2003a)

in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver (Yamauchi *et al.*, 2003b). AdipoR1 has been reported to have greater binding affinity to the globular domain of adiponectin while AdipoR2 binds to both the globular and full-length adiponectin with intermediate affinity (Yamauchi *et al.*, 2003b). While, a low degree of homology exists between AdipoR1 and AdipoR2 mRNA nucleotide sequences, both AdipoR1 and AdipoR2 have been found to be highly conserved molecules in several animals including the chicken (Ramachandran *et al.*, 2007). AdipoR1 and AdipoR2 appeared to be integral membrane proteins; the N terminus was internal and the C terminus was external, which is opposite to the topology of all other reported G protein-coupled receptors (Fig. 2) (Yamauchi *et al.*, 2003b; Kadowaki and Yamauchi, 2005).

## RELATIVE QUANTITY OF ADIPOR1 AND ADIPOR2 MRNA IN VARIOUS TISSUES

Skeletal muscle, adipose tissue and diencephalon was found to contain the highest quantities of AdipoR1 RNA followed by kidney, ovary, liver, anterior pituitary and spleen. AdipoR1 expression in the diencephalon may suggest its involvement in adiponectin signaling possibly in the hypothalamus. In this regard, intracerebroventricular administration of adiponectin has been found to affect energy metabolism and body weight in mice (Qi *et al.*, 2004). Adipose tissue had the highest quantity of AdipoR2 mRNA followed by skeletal muscle, liver, ovary, diencephalon, anterior pituitary, kidney and spleen. AdipoR2 mRNA expressed in the chicken liver may possibly be involved in lipid metabolism, glucose utilization and gluconeogenesis. Adiponectin receptors (both AdipoR1 and AdipoR2) expressed in skeletal muscle are possibly involved in glucose utilization as in mammals and also in thermogenesis as chicken skeletal muscle fast twitch fibers convert to slow twitch fibers for heat production when exposed to cold (Hirabayashi *et al.*, 2005).

## EFFECT OF FEED DEPRIVATION ON ADIPOR1 MRNA OR ADIPOR2 MRNA QUANTITY

Feed deprivation for 48 h resulted in a significant decrease ($p<0.05$) in AdipoR1 mRNA quantity in the anterior pituitary gland but not in adipose tissue, diencephalon and liver . Similarly, AdipoR2 mRNA content was significantly increased ($p<0.05$) in adipose tissue due to a 48 h feed deprivation, while its quantity remained unchanged in liver, diencephalon and anterior pituitary gland. Feed deprivation is likely to create a negative energy balance that may have altered expression of the AdipoR1 or AdipoR2 genes in these organs involved in metabolism or neuroendocrine system. A significant change in AdipoR1 or AdipoR2 mRNA quantity and a concomitant decrease in adiponectin mRNA quantity in response to fasting suggest that adiponectin may possibly regulate its own secretion from adipose tissue and/or from pituitary gland in an autocrine and/or paracrine regulatory pathway. A significant increase in AdipoR2 gene expression in adipose tissue due to fasting in the chicken may possibly be due to decreased plasma insulin levels that normally occur during fasting in the chicken (Krestel-Rickert *et al.*, 1986; Ramachandran *et al.*, 2007). In contrast, a decrease in AdipoR1 gene expression in the pituitary gland may suggest that its gene expression is apparently not under the control of insulin (Staiger *et al.*, 2004).

## REGULATION OF ADIPONECTIN SECRETION AND MRNA EXPRESSION

Through the stimulation of AdipoR1 or AdipoR2, adiponectin has been found to activate cyclic adenosine monophosphate-activated protein kinase (PRKAA2) (Yamauchi *et al.*, 2002) resulting in the phosphorylation of various intracellular proteins including acetyl-coenzymeAcarboxylase (ACACA) and peroxisome proliferatoractivated receptor a (Fruebis *et al.*, 2001; Yamauchi *et al.*, 2003a). Adiponectin stimulates fatty acid oxidation through phosphorylation and inhibition of ACACA and activation of malonyl-coenzyme A (malonyl-CoA) decarboxylase resulting in reduced malonyl-CoA content. A decrease in malonyl-CoA concentration increases the transport of long chain fatty acyl-CoA molecules into the mitochondria where they are oxidized (Tomas *et al.*, 2002). Furthermore, adiponectin has been found to activate the MAP kinase (MAPK) pathway in the placenta (Lappas *et al.*, 2005), vascular tissue (Arita *et al.*, 2002; Shibata *et al.*, 2005) and osteoblasts (Luo *et al.*, 2005). Adiponectin is likely to play a dominant role in carbohydrate and lipid metabolism in avian species because chickens maintain a very high blood glucose concentration (Brady *et al.*, 1978). In addition, a majority of the lipids in the chicken are synthesized in the liver but not in the adipose tissue as in mammals (Leveille *et al.*, 1975).

## ROLE OF ADIPONECTIN ON CARBOHYDRATE AND LIPID METABOLISM IN THE CHICKEN

Adiponectin plays a dominant role in lipid and carbohydrate metabolism. Indeed, adiponectin stimulates fatty acid oxidation, decreases plasma triglycerides and improves glucose metabolism by increasing insulin sensitivity (Yamauchi *et al.*, 2002). Adiponectin is also involved in the regulation of energy balance and body weight (Yamauchi *et al.*, 2001; Fruebis *et al.*, 2001) and has direct antiatherosclerotic effects (Kadowaki and Yamauchi, 2005). The synthesis and secretion of adiponectin is regulated by several factors including IGF-1 and insulin (Halleux *et al.*, 2001), thiazolidinediones (Bodles *et al.*, 2006) and testosterone (Berra *et al.*, 2006; Page *et al.*, 2005).

## PHYSIOLOGICAL ROLE OF ADIPONECTIN AND ITS RECEPTORS IN THE OVARY

Chabrolle *et al.* (2007) reported that adiponectin, AdipoR1 and AdipoR2 mRNAs were expressed in chicken granulosa and theca cells. Adiponectin mRNA expressionwas 10-to 30-fold higher in theca cells than in granulosa cells whereas AdipoR1 mRNA was two-fold more expressed in granulosa cells than in theca cells. In chicken, we do not know yet if the thecal adiponectin mRNA is translated and the adiponectin protein is secreted. However, they hypothesize that adiponectin produced in thecal cells exerts autocrine and/or paracrine effects on the ovarian functions. For example, it could contribute to regulate the production of androgens and steroids in theca and granulose cells, respectively. Indeed, they have shown that human recombinant adiponectin (10 g mL$^{-1}$) increased IGF-1 induced progesterone secretion in F2 and F3/4 granulosa cells and decreased LH-or FSH-induced progesterone production in F3/4 granulosa cells. The molecular mechanisms involved in the effects of adiponectin on the chicken granulosa cells are under investigation. However, in mammals, adiponectin is known to increase insulin sensitivity in peripheral tissues and consequently the increase of the progesterone secretion in the presence of IGF-1 and in response to adiponectin in chicken granulose cells is not surprising. In mammals, this insulinsensitizing action of adiponectin occurs through activation of AMPK (Yamauchi *et al.*, 2002). The AMPK activation is able to enhance insulin signaling in a PI3K/Akt pathway-dependent or independent manner (Chen *et al.*, 2002). Chabrolle *et al.* (2007) reported an activation of AMPK in response to adiponectin in chicken cultured granulosa cells. They have observed that AMPK activation reduced progesterone secretion (Tosca *et al.*, 2006). Also, adiponectin reduced FSH-induced progesterone secretion in F3/4 granulosa cells. Negative effects of testosterone indicated on circulating adiponectin in humans (Berra *et al.*, 2006; Page *et al.*, 2005; Lanfranco *et al.*, 2004) and mice (Nishizawa *et al.*, 2002).

## PHYSIOLOGICAL ROLE OF ADIPONECTIN AND ITS RECEPTORS IN TESTICULAR FUNCTION

Ocon-Grove *et al.* (2008) indicated that adiponectin and its receptors are expressed in the chicken testis, where they are likely to influence steroidogenesis, spermatogenesis, Sertoli cell function as well as spermatozoa motility. Testicular adiponectin may likely act as a paracrine/autocrine factor thereby supplementing blood-borne adiponectin in order to influence various functions of cells within seminiferous tubules and interstitial cells in the chicken. Also, Ocon-Grove *et al.* (2008) found that both adiponectin and AdipoR1-ir cells were located in the peritubular cells and Leydig cells surrounding the seminiferous tubules. In the chicken testis, based on distinguishable flattened cell morphology of the peritubular cells, adiponectin and AdipoR1 appear to be expressed in peritubular myoid cells. The localization of both adiponectin and AdipoR1 in peritubular cells indicate that adiponectin is likely to influence myoid cell function. Peritubular myoid cells are involved in the transport of spermatozoa and testicular fluid from the seminiferous tubule (Maekawa *et al.*, 1996), secretion of extracellular matrix proteins such as fibronectin (Galdieri and Ricci, 1998) and regulation of Sertoli cell function (Tung and Fritz, 1980; Maekawa *et al.*, 1996). In addition to myoid cells, the peritubular space also contains immune cells such as macrophages (Hutson, 1994). It is, therefore, likely that some of the peritubular cells expressing AdipoR1 protein may be macrophages influenced by adiponectin elsewhere (Yokota *et al.*, 2000; Hales, 2002). One of the functions of peritubular macrophages is to secrete another adipokine hormone, tumor necrosis factor-a, that plays a major role in controlling Leydig cell function (Hales, 2002). AdipoR2 immunoreactivity was predominantly observed in the Leydig cells as well as in the adluminal and luminal compartments of the chicken seminiferous tubules. Intense AdipoR2 immunostaining was observed along the Sertoli cell syncytia, suggesting a potential role of adiponectin in regulating Sertoli cell function. Furthermore, AdipoR2 immunostaining was noticed in the round spermatids, elongating spermatids and spermatozoa. Based on such widespread AdipoR2 immunostaining throughout the adluminal and luminal compartments of the seminiferous tubule, Ocon-Grove *et al.* (2008) hypothesize that adiponectin is involved in maturation and differentiation of spermatocytes and therefore, potentially influences spermatogenesis. Adiponectin is also likely to affect metabolism of cells within the seminiferous tubules, possibly through an activation of PRKAA2 and peroxisome proliferator-activated receptors that have been previously identified in mammalian testis tissues (Cheung *et al.*, 2000;

Froment *et al.*, 2006). Adiponectin is also likely to affect sperm motility as our immunohistochemical data suggest that AdipoR2 is expressed in the flagella of spermatozoa found in the seminiferous tubular lumen. Testicular AdipoR1 and AdipoR2 mRNA quantities were 8.3 and 9-fold higher in adult chickens than prepubertal chickens respectively, suggesting that sexual maturation is associated with up-regulation of AdipoR1 and AdipoR2 gene expressions. Prepubertal chickens and adult chickens were raised under different photoperiod and feeding regimen to discourage hyperphagia and rapid growth that are detrimental to reproductive performance. Therefore, the observed up-regulation in AdipoR1 and AdipoR2 mRNA levels in adult chicken may have resulted from a combination of factors such as changes in photoperiod, feeding schedule or age. Significant elevation of AdipoR1 and AdipoR2 gene expressions in sexually mature chickens is involved in supporting higher metabolic activity related to spermatogenesis, testicular steroid hormone production and transport of spermatozoa and testicular fluid (Ocon-Grove *et al.*, 2008).

## GOOSE ADIPONECTIN GENE

The coding sequence and the goose adiponectin protein shared the highest homology with duck adiponectin, which were 94.85%. The next highest homology was with chicken adiponectin and the lowest homology was with that of mammals. The predicted molecular weight of goose adiponectin protein were highly similar to those of other species. The adiponectin gene contained an N-signal peptide, a negative homology region, collagen repeated sequence and globular carboxy-terminus (Berg *et al.*, 2002). In the negative homology region, the goose adiponectin amino acids from the N-terminus were lower in homology to those of other species, except duck adiponectin which is a waterfowl too. In the collagen repeated sequence region, 22 Gly-X-Y structures, which were present in the adiponectin of mammals, chicken and duck, were also found in the goose adiponectin (Guo-Qing *et al.*, 2009).

## MRNA EXPRESSION LEVEL IN VARIOUS TISSUES

Semi-quantitative RT-PCR results from Guo-Qing *et al.* (2009) indicated that the goose adiponectin mRNA was highly expressed in skeletal muscle, adipose, heart and muscular stomach, moderately expressed in the small intestine, glandular stomach, kidney, lung and weakly expressed in the liver, spleen, diencephalon and ovary. Semi-quantitative RT-PCR results from Yuan *et al.* (2006) indicated that the chicken adiponectin mRNA displayed high expression levels in adipose, heart, stomach and skin and weak expression in skeletal muscle. This reveals that adiponectin has a broad function in life. Genetic variance among species in considered to be the main reason for the differential expression of the adiponectin gene in these species.

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