Journal of Advanced Veterinary and Animal Research
ISSN 2311-7710 (Electronic)
http://doi.org/10.5455/javar.2016.c158
A periodical of the Network for the Veterinarians of Bangladesh (BDvetNET)

September 2016
Vol 3 No 3, Pages 206-213.

Mini Review

Adipokines as metabolic modulators of ovarian functions in livestock: A mini-review

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• **Received:** June 11, 2016 • **Revised:** July 13, 2016 • **Accepted:** July 13, 2016 • **Published Online:** July 21, 2016

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ABSTRACT

Adipose tissue is the principal fat storing tissue which secretes various molecules known as adipokines. The major adipokines secreted from adipose tissue are leptin, adiponectin, visfatin, resistin, chemerin and apelin. Adipokines are regarded as the "*marker of body metabolic status*" which maintains the body energy homeostasis. An adequate energy level is essential for the onset of puberty and ovarian functions. Adipokines act as energy sensor and signal the body energy level to hypothalamic neurons to regulate many physiological activities including ovarian functions such as onset of puberty, estrus behavior, follicular development and ovulation followed by corpus luteum (CL) formation and function in livestock. However, adipose tissue dysfunctions limit adipokines secretion leading to an imbalance in body energy level which ultimately affects the reproduction in livestock. This mini-review highlights the modulatory roles of various adipokines in ovarian functions of livestock.

KEYWORDS

Adipose tissue, Adipokines, Livestock, Ovarian functions

How to cite: **Mishra SR, Bharati J, Bharti MK, Kar D, Sahoo PR (2016). Adipokines as metabolic modulators of ovarian functions in livestock: A mini-review. Journal of Advanced Veterinary and Animal Research, 3(3): 206-213.**

INTRODUCTION

Adipose tissue comprises of fat storing cells or adipocytes which secretes variety of metabolic factors known as adipokines and considered as the largest endocrine gland in the body (Ahima, 2006). Chief adipokines secreted from adipose tissue are leptin, adiponectin, resistin, visfatin, chemerin and apelin etc. (Tsatsanis et al., 2015). Normally adipokines control body metabolism (mostly lipid and glucose metabolism) and mediate insulin action in peripheral tissues thereby maintains body energy homeostasis (Badman and Flier, 2007; Bohler et al., 2010; Lee and Shao, 2013). Apart from general physiological functions, adipokines are thought to be involved in regulation of ovarian dynamics and functions in livestock (Campos et al., 2008). Adipkoines signal body metabolic status to hypothalamic neurons and acts on hypothalamo-pituitary gonadal (HPG) axis to regulate reproduction in livestock (Tsatsanis et al., 2015).

Ovarian dynamics characterized by repeated patterns of cellular proliferation, differentiation and transformation of ovarian follicular cells that accompany folliculogenesis and ovulation followed by formation and function of the corpus luteum (CL) (Berisha and Schams, 2005). A bidirectional communication exists between oocyte and granulosa cell (GC) as well as GC and theca cell which is necessary for proper follicular development and ovarian functions (Binelli and Murphy, 2010). Optimum body energy level is an important factor for the onset of puberty, sexual maturity and fertility in domestic animals (Mitchell et al., 2005). Adipokines signal the body nutritional level and fat reserve to hypothalamic neurons and control ovarian functions like onset of puberty, estrous behavior, follicular development and ovulation in livestock (Budak et al., 2006; Mircea et al., 2007; Tersigni et al., 2011; Dupont et al., 2013). Based on the earlier findings, adipokines are the candidate molecules which link body metabolic status and initiate repro-duction in most domestic species. Therefore, the present review summarizes the effect of adipokines on ovarian functions in livestock.

LEPTIN

Leptin (16 kDa) is the most predominant adipokine secreted from white adipocytes (Bohler et al., 2010; Mishra and Palai, 2014). Leptin secretion increases during fed state while decreases during fasting period (Mitchell et al., 2005). Leptin acts as a connecting link between adipose tissue and female reproduction (Brann et al., 2002). Leptin binds to its receptor (Ob-R) in preoptic neurons of hypothalamus and decreases neuropeptide-Y (NPY) and agouti regulated protein (AgRP) expression while promotes pro-opiomelanocortin (POMC)/alfa-melanocyte stimulating hormone (α-MSH) and cocaine-amphetamine related protein (CART) expression to induce reproduction in farm animals and humans (Mishra and Palai, 2014; Tsatsanis et al., 2015). Leptin stimulates GnRH production via kisspeptin neurons located in arcuate nucleus of hypothalamus (Backholer et al., 2015) thus plays a crucial role in initiation of puberty (Plant, 2013; Pinilla et al., 2015). Leptin and Ob-R are expressed in ovarian follicle and CL of human (Karlsson et al., 1997), rat (Archanco et al., 2007), cattle (Sarkar et al., 2010) and buffalo (Kumar et al., 2012). Leptin stimulates gonadotropin secretion and ovarian steroidogenesis in human (Agarwal et al., 1999), rat (Dagklis et al., 2014), pig (Ruiz-Cortes et al., 2003) and cattle (Amstalden et al., 2003). Leptin expression is higher in luteal phase compared to follicular phase in human ovary (Einollahi et al., 2014). Leptin-deficient mice fail to secrete gonado-tropin releasing hormone (GnRH) and gonadotropins (Quennell et al., 2009) with subsequent reduction of estradiol (E_2) secretion in rat follicular cells (Farooqi, 2002). However, leptin administration resumes puberty in human (Von Schnurbein et al., 2014) and mice (Chehab et al., 1997; Ryan et al., 2002).

ADIPONECTIN

Adiponectin (30kDa) is secreted from white adipocytes (Trujillo and Scherer, 2005). It is also known as adipocyte complement-related protein 30 kDa (Acrp30) or adipose most abundant gene transcript-1 (apMI) or gelatin-binding protein (GBP 28) (Kadowaki and Yamauchi, 2005). Unlike leptin, serum adiponectin level decreases with obesity (Gavrila et al., 2003) and increases during dietary restriction and fasting period (Baratta et al., 2004). Adiponectin stimulates insulin sensitivity in skeletal myocytes and hepatocytes (Berg et al., 2001; Lihn et al., 2005). Adiponectin mediates its effect through adiponectin receptor 1 (AdipoR1), adipokine receptor 2 (AdipoR2) and T-cadherin receptor (Kadowaki et al., 2006). AdipoR1 is expressed in almost all tissues including skeletal myocytes and lateral hypothalamus whereas AdipoR2 is mostly expressed in hepatocytes and brown adipocytes (Psilopanagioti et al., 2009).

Adiponectin concentration is higher in follicular fluid (FF) of human (Chabrolle et al., 2009) and sow (Ledoux et al., 2006). Luteinizing hormone (LH) increases adipo-nectin level in follicular fluids and stimulates insulin activity in human ovarian cells (Gutman et al., 2009). Adiponectin is expressed in somatic cell types, germ cells and CL of ovary in various domestic species. Adiponectin is expressed in oocyte and CL of rat (Chabrolle et al., 2007a). It is also expressed in theca cell of chicken

(Chabrolle et al., 2007) and rat (Chabrolle et al., 2007a). However, it does not express in GC of rat (Chabrolle et al., 2007a), chicken (Chabrolle et al., 2007), human (Chabrolle et al., 2009) and pig (Ledoux et al., 2006). Adiponectin mRNA expression is higher in GC of preovulatory follicle (PF) whereas its expression is higher in theca cell of primary follicle in chicken (Chabrolle et al., 2007). Overall, adiponectin mRNA expression is 20 fold higher in theca cell compared to GC of chicken (Chabrolle et al., 2007). Adiponectin improves oocyte development and maturation in mice and human (Richards et al., 2012). Adiponectin stimulates ovulation via activation of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), prostaglandin E2 (PGE2) and cyclo-oxygenase 2 (COX2) in pig (Ledoux et al., 2006). Adiponectin and insulin like growth factor I (IGF-I) combo stimulate E_2 and progesterone (P_4) secretion in GC of rat (Chabrolle et al., 2007a) and human (Chabrolle et al., 2009). Adiponectin and IGF-I combo stimulates GC steroidogenesis while do not stimulate GC proliferation in human (Chabrolle et al., 2009). Adiponectin and IGF-I combo increases GC steroidogenesis and proliferation however, does not affect oocyte development in cattle (Maillard et al., 2010). Adiponectin regulates human folliculogenesis and ovulation while adiponectin with follicle stimulating hormone (FSH) promote superovulation in human (Liu et al., 2006). Adiponectin down-regulates rate limiting enzymes such as cytochrome P450 side chain cleavage (CYP11A1) and 17 α-hydroxylase (CYP17A1) thereby inhibits theca cell androgen production in cattle (Lagaly et al., 2008; Comim et al., 2013). Adiponectin promotes IGF-I induced P_4 secretion human (Wickham et al., 2014) but do not affect E_2 secretion in chicken (Chabrolle et al., 2007) rat (Mansour et al., 2009) ovary.

AdipoR1 and AdipoR2 are expressed in ovarian follicular cells of rat (Chabrolle et al., 2007a), chicken (Chabrolle et al., 2007), human (Chabrolle et al., 2009), pig (Lord et al., 2005) and cattle (Maillard et al., 2010). AdipoR1 mRNA expression is higher in GC and theca cell while AdipoR2 mRNA expression is higher in oocyte of developing follicles in cattle (Tabandeh et al., 2010). Gonadotropin administration up-regulates AdipoR1 expression thereby stimulates follicular development and ovulation in chicken (Chabrolle et al., 2007). Gonadotropins modulate AdipoR2 expression and stimulate 3 beta hydroxy steroid dehydrogenase (3βHSD) expression thereby increase P_4 secretion in human GC (Wickham et al., 2014). Gene knockdown of AdipoR1 and AdipoR2 stimulates apoptosis and inhibits steroidogenesis in cultured human GC respectively (Pierre et al., 2009). Adiponectin receptors are expressed significantly higher in luteal phase of menstrual cycle in human (Takemura et al., 2006).

RESISTIN

Resistin (12 kDa) was first identified in mice adipocytes (Schwartz and Lazar, 2011). It prevents insulin activity in adipocytes, skeletal myocytes and hepatocytes thus cause insulin resistance and obesity in rat (Satoh et al., 2004). Resistin is expressed in GC and theca cells in rat (Maillard et al., 2011), human (Niles et al., 2012; Reverchon et al., 2013a) and cattle (Maillard et al., 2011). Resistin inhibits GC steroidogenesis in smaller follicles while enhance GC proliferation in larger follicles of cattle (Spicer et al., 2011). The combination of resistin and IGF-I modulate GC proliferation and steroidogenesis in cattle and rat (Maillard et al., 2011). However, resistin and IGF-I combo does not show any effect on theca cell steroidogenesis in cattle (Spicer et al., 2011). Resistin regulates theca cell steroidogenesis by stimulating CYP17A1 expression in cultured human theca cell (Munir et al., 2005). Resistin stimulates the key steroidogenic factors *viz*.. cytochrome P450 side chain cleavage enzyme CYP11A1, 3βHSD, CYP17A1 and 17 beta hydroxyl steroid dehydrogenase (17βHSD) thereby modulates theca cell androgen production while, recombinant resistin does not affect aromatase (CYP19A1) expression and E_2 secretion in pig ovarian follicle (Rak-Mardy et al., 2013). Steroids and gonadotropins enhance whereas IGF-I inhibits resistin production from ovarian follicle of pig (Rak et al., 2015). Resistin decreases ovarian steroidogenesis in cattle (Reverchon et al., 2015a; Spicer et al., 2015).

VISFATIN

Visfatin (52 kDa) is also known as pre B cell enhancing factor (PBEF) or nicotinamide phosphoribosyl transferase (Nampt) (Stephens and Vidal-Puig, 2006; Dahl et al., 2012). It mostly expressed in visceral adipose tissue including liver, bone marrow, skeletal muscle, lymphocytes, and trophoblast cells (Kendal and Bryant-Greenwood, 2007; Dahl et al., 2012). It mimics insulin and stimulates glucose uptake in skeletal myocytes and adipocytes (Fukuhara et al., 2005; Bohler et al., 2010; El-Mesallamy et al., 2013). Its expression is up regulated during obesity and type II diabetes (Beltowski, 2006; Chen et al., 2006a). Visfatin is localized GC, oocyte, cumulus cell, and theca cell of human ovarian follicle (Reverchon et al., 2013). Visfatin regulates follicular growth, maturation of oocytes, dominance and ovulation in human ovary (Shen et al., 2010). Visfatin and IGF-I combo induce GC proliferation and steroidogenesis in human ovary (Reverchon et al., 2013). Metformin human ovary (Reverchon et al., 2013). Metformin modulates the visfatin expression in human GC (Reverchon et al., 2013).

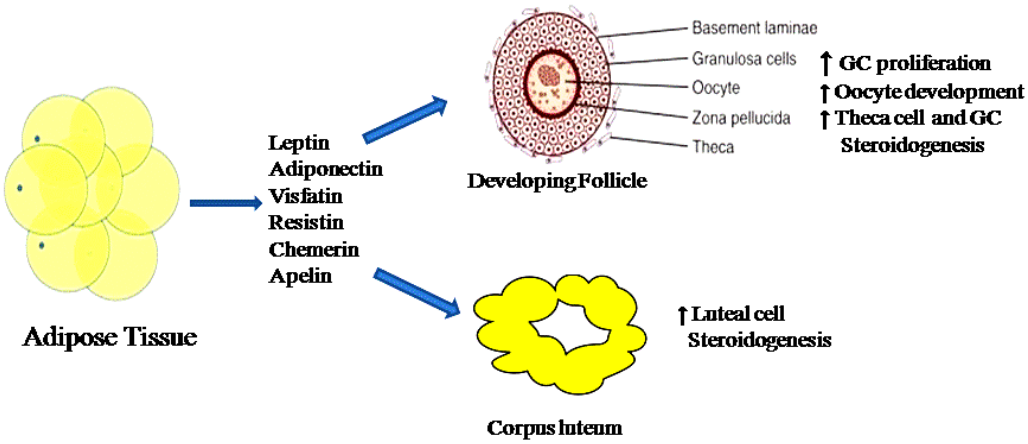

Figure 1: Role of Adipokines on ovarian functions

Human chorionic gonadotropin (hCG) and PGE_2 enhance visfatin expression in human GC (Shen et al., 2010). Visfatin promotes oocyte deve-lopmental competence and superovulation in mice (Choi et al., 2012).

CHEMERIN

Chemerin (14 kDa) regulates insulin sensitivity in peripheral tissues (Ernst et al., 2014; Yu et al., 2015). Chemerin and its receptors (chemokine-like receptor 1, CMKLR1) are expressed in monocytes, macrophages and certain immune cells like natural killer cells and dendritic cells (Parolini et al., 2007). Chemerin and its receptor are expressed in ovarian cells rat (Wang et al., 2015), human (Reverchon et al., 2012) and cattle (Reverchon et al., 2015a). Chemarin and its receptor are expressed in GC, theca cell and follicular fluid of human ovary (Reverchon et al., 2012). Chemarin and its receptor are localized in GC, theca cell, CL and oocyte of cattle (Reverchon et al., 2015a). Chemerin inhibits ovarian steroidogenesis (Wang et al., 2015) and GC apoptosis in rat (Kim et al., 2013). Chronic administration of androgen induces follicular atresia in antral follicle of rat (Kim et al., 2013). Chemerin also inhibits ovarian steroidogenesis in cattle (Reverchon et al., 2015a; Spicer et al., 2015). Chemerin inhibits IGF-I induced E_2 and P_4 secretion in cultured GC of human (Reverchon et al., 2012). Chemerin also down-regulates CYP19A1 expression followed by decrease E_2 secretion in GC (Ballinger et al., 2003). Chemerin decreases growth differentiation factor 9 (GDF9) expression which promote GC proliferation in preantral follicles of rat (Reverchon et al., 2014).

APELIN

Apelin is secreted from adipocytes and vascular stromal cells (Tatemoto et al., 1998). Which stimulates endothelial cell (EC) proliferation and migration thereby stimulates angiogenesis (Tatemoto et al., 1998). Apelin secretion increase during obesity and stimulates insulin resistance (Dupont et al., 2012). Apelin and its receptor (APJ) are expressed in theca cell while APJ is mostly expressed in GC of cattle (Shimizu et al., 2009). Apelin and APJ are be involved in follicular dominance and ovulation in cattle (Schilffarth et al., 2009). However, higher expression of APJ in GC results in follicular atresia in cattle (Shimizu et al., 2009).

CONCLUSION

Adipose tissue is the store house of various adipokines which maintains the body energy homeostasis. Optimum body nutrition level is indispensible for normal physiological activities including ovarian functions while inadequate nutrition impairs reproduction and reproductive potential of livestock. Adipokines convey body metabolic status to hypothalamic neurons to regulate ovarian functions as well as reproduction in livestock. Though adipokines are involved in regulation of ovarian functions but the detail molecular mechanism in many domestic species is yet to be clearly elucidated. Therefore, further research investigations need to be undertaken to unveil the exact mechanism of actions and signalling pathway of adipokines in ovarian dynamics and functions which might improve the reproductive efficiency as well as production and productivity of livestock.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENT

We thank Dr. AK Kundu, Professor and Head, Department of Veterinary Physiology for final check-up and proof reading of this review paper.

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