OPEN ACCESS INTERNATIONAL JOURNAL OF SCIENCE & ENGINEERING

A NOVEL STRATEGY FOR INSULIN RESISTANCE: INTERACTIVE ROLE OF INSULIN WITH OTHER HORMONES

Bindulekha D.S
Department of Zoology, Christian College, Kattakada, Kerala, India
binduhaiya@gmail.com

Abstract: **As a metabolic hormone insulin regulates an impressive spectrum of physiological processes. Hormones do not act only in a linear pathway. Hormonal pathways are interconnected by a complex network of interactions and feedback circuits that determines the final outcome of the individual hormone actions. Insulin resistance is controlled by many regulatory actions and this article will highlight the interaction of different hormones with insulin and how the process may be impaired in the insulin resistant state. These interactions either potentiate or reduce the biological actions of insulin and, therefore, attenuate or induce insulin resistance.**

Keywords: *Insulin, insulin resistance, glucose homeostasis, metabolism, hormones*

----------∴∴∴----------

I INTRODUCTION

Insulin, an anabolic polypeptide hormone, has a multitude of actions on a wide range of cellular processes in vertebrates. Insulin resistance is characterized by the lack of biological responsiveness to endogenous or exogenous insulin. Insulin resistance occurs when some aspects of the insulin receptor-intracellular cascade stop responding normally to insulin and the body as a whole becomes less sensitive to insulin (Treiber *et al*., 2006). It is most likely the outcome of both polygenic flaws and environmental influences (Qin *et al*., 2003). This resistance to normal amounts of insulin causes the pancreas to produce increasing amounts of insulin in order to keep blood glucose at a normal level, meaning higher concentrations of insulin are required to keep glucose at the same level (Treiber *et al*., 2006).

Many bodily factors can compromise the standard physiologic reaction to glucose (Qin *et al*., 2003). In humans, over 50 mutations of the insulin receptor gene have been characterized (Tritos and Mantzoros, 1998). Mechanisms of these mutations can be grouped into three divisions involving receptor, pre-receptor and post-receptor insulin resistance (Chang *et al*., 2004). When the number or avidity of insulin receptors declines, receptor type insulin resistance occurs. Pre-receptor insulin resistance, on the other hand, occurs when circulating antibodies are developed against insulin receptors, causing insulin to not bind to the target cells well (Chang *et al*., 2004). The third group, post-receptor type insulin resistance, is the most common type of insulin resistance. This type is caused by a signaling failure by intracellular effectors of insulin's actions (Chang *et al*., 2004). These receptor failures can cause serious problems in vertebrates. With insulin resistance, the body is forced to produce greater amounts of insulin to signal the target tissues to incorporate glucose transport proteins in the face of hyperglycemia (Frank *et al*., 2006). Sustained hyperglycemia from insulin resistance may ultimately overpower the pancreas ability to produce insulin (Chang *et al*., 2004) and that results in Type I diabetes.

Several hormones including sex hormones, cortisol, aldosterone and epinephrine have modes of action that either potentiate or reduce the biological actions of insulin and, therefore, attenuate or induce insulin resistance. Since insulin action may be modified, these hormones potentially contribute to the modifications of metabolic pathways. The purpose of this review is to discuss the interactions of various hormones that modulate insulin action results in insulin resistance. Given the breadth of the topic, this review will not be exhaustive, but it points out the diverse areas of current understanding of this continuously emerging field.

II INSULIN RESISTANCE AND ESTROGEN

Various clinical observations and experimental data from *in vitro* studies suggest that insulin and sex hormones interact on carbohydrate metabolism (Polderman *et al*., 1994). These sexual steroids has effects on peripheral tissues, and since the skeletal muscle is the main responsible for

peripheral glucose uptake, it would be possible that the sexual steroids induce directly in the muscle a decrease of the sensibility of this tissue to insulin action(Alonso and Gonzalez, 2008). Among sex steroids, estrogens are important participants in metabolic regulation.

Estrogen receptors, ERα and ERβ, are important molecules involved in glucose metabolism, yet their role in pancreatic β-cell physiology is still greatly unknown (Alonso-Magdalena *et al*., 2008). Previous studies showed that both ERα and ERβ are present in pancreatic β-cells. Long term exposure to physiological concentrations of 17β-estradiol (E2) increased β-cell insulin content, insulin gene expression and insulin release, yet pancreatic β-cell mass was unaltered (Alonso-Magdalena *et al*., 2008). Clinical trials and animal studies have revealed that loss of circulating estrogen induces rapid changes in whole body metabolism, fat distribution, and insulin action. The metabolic effects of estrogen are mediated primarily by its receptor, estrogen receptor-α and it is thought to have a positive effect on insulin signaling and GLUT4 expression in the skeletal muscle (Barros *et al*., 2009; 2006) however, the detailed understanding of its mechanisms is incomplete. Similarly the prodiabetogenic ERβ may also cause reduced GLUT4 expression (Barros *et al*., 2009; 2006). Recent investigations suggest that estrogen receptor-α elicits the metabolic effects of estrogen by genomic, nongenomic, and mitochondrial mechanisms that regulate insulin signaling, substrate oxidation, and energetics (Anisha *et al*., 2015).

Estrogen may regulate insulin action directly *via* actions on insulin-sensitive tissues or indirectly by regulating factors like oxidative stress, which contribute to insulin resistance. Effects of estrogen in metabolism are also centrally controlled at the level of the hypothalamus regulating appetite (Clegg *et al*., 2006), and thus in the case of obesity due to increased appetite in E2-deficiency contributes to reduced insulin sensitivity. In short, estrogen deficiency promotes metabolic dysfunction predisposing to obesity, the metabolic syndrome, and type 2 diabetes. Ribas *et al*. (2010) suggested a protective effect of estrogen on insulin action via reduction of inflammation (Ribas *et al.*, 2010). It has been proposed a major role of estrogens in control of energy balance and glucose homeostasis. Similarly, estrogen actions in skeletal muscle, liver, adipose tissue, and immune cells are involved in insulin sensitivity as well as prevention of lipid accumulation and inflammation (Mauvais-Jarvis *et al*., 2013). Likewise, estrogen actions in pancreatic islet β-cells also regulate insulin secretion, nutrient homeostasis, and survival. Similarly, hematopoietic or myeloid-specific ERα exerts important effects on global insulin action and MetS (Ribas *et al*., 2011).

There are several studies reporting that ovarian steroids affect β -cell function and glucose homeostasis by increasing insulin production through the induction of β -cell hypertrophy (Nieuwenhuizen *et al*., 1999; Gonzalez *et al*., 2000). It has been proposed that a nonsteroidal hormone such as insulin may directly exert an influence through estrogen receptors and alter the biologic behavior of steroid hormone target tissue (Chaudhuri *et al*., 1986). Estrogen has been shown to have profound effects on insulin and glucose metabolism *in vivo*. Indeed, estrogens were recently shown to modulate ion channel and secretory activities in endocrine cells (Horn *et al*., 2000). All these data thus support that responses to estrogens on insulin resistance and glucose metabolism may result from indirect rather than direct betacytotropic effects (Horn *et al.*, 2000).

III INSULIN RESISTANCE AND PROGESTERONE:

Progesterone is the main pro-gestational steroid hormone secreted by the female reproductive system. To date only limited information is known about the influence of progesterone on insulin resistance in vertebrates. In the light of the clamp experiments demonstrated by Gonzalez *et al*. (2000), it has been suggested that the absence of female steroid hormones gives rise to decreased insulin sensitivity. In addition, it has been proposed that the action of progesterone on insulin sensitivity is focused on the insulin receptor, and thus reported that the amount of insulin receptor in the liver could be modified by the concentration of sex hormones. It is well documented that insulin sensitivity is influenced by sex hormone concentration, so progesterone per second increases insulin sensitivity at high concentrations (Gonzalez *et al*., 2000). However, a membrane delimited, non-genomic action of progesterone which inhibits insulin secretion was also suggested by Straub *et al*. (2001) and it has been reported that the steroid acts at the outer surface of the beta-cell plasma membrane.

IV INSULIN RESISTANCE AND TESTOSTERONE

Testosterone, the most important androgen plays a key role in reproductive and sexual function in men. Grillo *et al*. (2005) reported that testosterone rapidly stimulates insulin release from isolated pancreatic islets through a non-genomic dependent mechanism (Grillo *et al*., 2005). The study demonstrated the action of testosterone on the Ca^{2+} uptake and insulin secretion in short-term experiments using isolated pancreatic islets of Langerhans. Moreover, in these isolated pancreatic islets, physiological concentration of testosterone rapidly stimulate insulin secretion and Ca^{2+} uptake through a membrane bound mechanism (Grillo *et al*., 2005). In another study, Mootha *et al.* (2005) examined the relationship between serum testosterone levels and insulin resistance and mitochondrial function especially, OXPHOS gene expression in men. Their experiment demonstrated a positive correlation between serum testosterone levels and insulin resistance in men across the full spectrum of glucose tolerance. Moreover, men with hypogonadal testosterone levels are twice as insulin

resistant as their eugonadal counterparts, and 90% fulfill criteria for the metabolic syndrome. From a clinical perspective, these data highlight the importance of performing a comprehensive metabolic evaluation in men with hypogonadism and suggests a novel molecular mechanism whereby testosterone might modulate insulin sensitivity in men (Mootha *et al*., 2005). Similar results were demonstrated by Rao *et al*. (2013). Interventional studies have shown beneficial effects of testosterone on components of the metabolic syndrome, type 2 diabetes mellitus and other insulin resistance. The results also provide evidence that testosterone is also involved in lipid homeostasis in major insulin-responsive target tissues, such as liver, adipose tissue and skeletal muscle (Rao *et al*., 2013). Similarly, biochemical evidence indicates that testosterone is involved in promoting glucose utilization by stimulating glucose uptake, glycolysis and mitochondrial oxidative phosphorylation.

An alternative explanation for the inverse relationship between testosterone and insulin is that insulin resistance is associated with a decrease in Leydig cell T secretion in men (Pitteloud *et al*., 2005). The available evidence suggests that this relationship may, in fact, be bidirectional. Insulin signaling in the brain plays an important role in regulating reproductive function (Bruning *et al*., 2000). Insulin promotes growth hormone releasing hormone (GnRH) secretion in a hypothalamic GnRH neuronal cell line (Burcelin *et al*., 2003) and stimulates gonadotropin secretion from pituitary cell cultures (Adashi *et al*., 1981) and T secretion from cultured Leydig cells (Bebakar *et al*., 1990., Lin *et al*., 1986). Recently, Agbecha and Usoro (2017) reported that testosterone production seems to be impaired by elevated insulin that accompanies insulin resistance. Normalization of testosterone in controlled diabetes points at diabetic control instead of testosterone replacement therapy in the management of hypogonadism in male Type 2 Diabetes.

V INSULIN RESISTANCE AND THYROID HORMONES

The effects of thyroid hormones have a large impact on glucose homeostasis (Brenta, 2011). Thyroid hormones exert both insulin agonistic and antagonistic actions in different organs. However, this occurs in a fine balance necessary for normal glucose metabolism. It has been previously reported that, despite an expected resistance towards the insulin inhibitory effect on gluconeogenesis, the transcription of several enzymes involved in lipid synthesis or lipid metabolism is increased in hyperinsulinemic, insulin-resistant mice (Becker *et al*., 2004). It has been shown that the hypothalamus can modulate endogenous glucose production by using functionally reciprocal sympathetic and parasympathetic autonomic outputs to the liver (Kalsbeek *et al*., 2004). Moreover, a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver has been proposed as a central pathway for modulation of hepatic glucose metabolism by thyroid hormone (Klieverik *et al*., 2009). A direct regulation on thyroid responsive genes at the target organ has been described and more recently an indirect effect involving hypothalamic pathways that regulate glucose metabolism *via* control of the sympathetic nervous system has been reported. Furthermore, thyroid hormone effects can be insulin agonistic, such as demonstrated in muscle or antagonistic such as observed in the liver.

The genomic actions of thyroid hormone and steroids depend upon primary interactions of the hormones with their specific nuclear receptor proteins. Though thyroid hormones (TH) have a significant role in regulating energy balance, metabolism of glucose, and lipids (Chubb *et al*., 2005), it oppose the action of insulin and stimulate the hepatic gluconeogenesis and glycogenolysis. Previous studies suggested that theses hormones up-regulate the expression of genes such as glucose transporter type-4 (GLUT--4) and phosphoglycerate kinase, involved in glucose transport and glycolysis, respectively, thus acting synergistically with insulin facilitating glucose disposal and utilization in peripheral tissues results in insulin sensitivity (Weinstein *et al*., 1994; Viguerie *et al*., 2002; Clement *et al*., 2002).

VI Insulin Resistance and Aldosterone

The most important physiological role of aldosterone is to control water homeostasis and electrolytes balance. High levels of adrenal aldosterone secretion cause hypertension, that is, primary aldosteronism, a well-known form of secondary hypertension. Experimental evidence suggests an interaction between aldosterone and insulin (Giacchetti *et al*., 2005). Aldosterone induces hypokalemia, which may modulate insulin secretion, has direct effects on insulin receptor function (Plavinik *et al*., 1992; Corry *et al*., 2003), causes pancreatic cell dysfunction or even apoptosis (Sowers *et al*., 2009), interferes with insulin signaling pathways, (Wada *et al*., 2009), and decreases insulin sensitivity in human adipocytes *in vitro* (Kraus *et al*., 2005). Moreover, aldosterone reduces the expression of insulin sensitizing factors, such as adiponectin and peroxisome proliferator-activated receptor, in obese, diabetic mice (Guo *et al*., 2008). Hypokalemia might be one of causes of insulin resistance (Sperling, 2006). However, there was no relationship of baseline plasma potassium level with development of insulin resistance, suggesting no role of hypokalemia for the association between aldosterone and development of insulin resistance (Kumagai *et al*., 2011).

Aldosterone also impairs glucose-stimulated insulin secretion in isolated pancreatic islets *via* reactive oxygen species in a mineralocorticoid receptor-independent manner. Aldosterone-induced mineralocorticoid receptor activation also impairs insulin sensitivity in adipocytes and skeletal

muscle. Similarly, Aldosterone may produce insulin resistance secondarily by altering potassium, increasing inflammatory cytokines, and reducing beneficial adipokines such as adiponectin (Luther, 2014). Recently, there is increasing interest in exploring inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) as a unifying mechanism between insulin resistance and other components of the metabolic syndrome (Sowers *et al*., 2009). Recent data suggest that elevations in plasma aldosterone levels are associated with the insulin resistance independent of other components of angiotensin II. This relationship has been observed in studies exploring the association between primary aldosteronism, in which there are low levels of renin activity and Angiotensin II, and insulin resistance (Sowers *et al*., 2009).

VII INSULIN RESISTANCE AND CORTISOL

Glucocorticoid hormones (mainly cortisol in man; corticosterone in rodents) are produced in the adrenal cortex under the control of the hypothalamic– pituitary–adrenal axis. They play a key role in regulating salt and water metabolism, blood pressure, immune function, gluconeogenesis, fat and protein breakdown, and mobilization of extrahepatic amino acids and ketone bodies, shows its effect as an insulin antagonist. In essence, glucocorticoids are most important at times of stress, when they provide a longer-term signal to damp many of the acute responses to illness and‘re-set’ metabolism in favour of providing substrates for oxidative metabolism (Andrews and Walker, 1999).

Glucocorticoids, especially cortisol are well known to induce whole-body insulin resistance. It suppresses insulin secretion from pancreatic beta cells. Biorntorp (1992) suggested that the insulin resistance caused by cortisol is elicited in a stepwise manner, starting with an inhibition in the glycogen synthesis system in insulin-sensitive muscles, later including all muscles as well as 2-deoxyglucose uptake. This occurs without changes in morphology (Biorntorp, 1992). Similarly, it has repeatedly been demonstrated that high plasma levels of glucocorticoids which may occur in response to stressful events increases the plasma glucose concentration (Yasuda and Kitabchi, 1980; Kahn *et al*., 1981; Caro and Armatruda, 1982; Yamada *et al*., 1993). Interestingly, cortisol is generally considered to be a permissive hormone in mammals, its direct effect is to allow other hormones to exert their effects (Vijayan and Leatherland, 1992).

VIII INSULIN RESISTANCE AND EPINEPHRINE

The adrenal medulla is a minor contributor to total circulating catecholamine’s though it contributes over 90% of circulating epinephrine. Little epinephrine is found in other tissues, mostly in scattered chromaffin cells. Epinephrine causes a prompt increase in blood glucose concentration in the post absorptive state (Sherwin and Sacca, 1984). This effect is mediated by a transient increase in hepatic glucose production and an inhibition of glucose disposal by insulin-dependent tissues. Epinephrine augments hepatic glucose production by stimulating glycogenolysis and gluconeogenesis. Although its effect on glycogenolysis rapidly wanes, hyperglycemia continues because the effects of epinephrine on gluconeogenesis and glucose disposal persist (Sherwin and Sacca, 1984).

Previous studies of man and animals have demonstrated that both endogenous release of epinephrine after stress as well as exogenous epinephrine infusion are known to result in impaired glucose tolerance (Deibert and Defronzo, 1980). This effect of epinephrine results from inhibition of insulin secretion and augmentation of hepatic glucose production or diminished tissue responsiveness to insulin. Similarly, insulin indirectly stimulates carbohydrate oxidation by facilitating glucose transport into the cells and lowering fatty acid levels, and that epinephrine favours lipid oxidation through its lipolytic effects and its suppression of insulin release suggests a major interactive role of insulin with epinephrine results in insulin resistance (Muller-Hess *et al*., 1975).

IX INSULIN RESISTANCE AND GH-IGF

Growth hormone (GH) exerts its actions through specific cell surface receptors (Leung *et al*., 1989). Although GH has both metabolic and anabolic actions, most of its anabolic actions are mediated through the generation of IGF-1(Mathews *et al*., 1988). IGF-1 has profound these anabolic and metabolic effects in many cell types, acting through autocrine, paracrine and classical endocrine mechanisms (Jones JI and Clemmons, 1995). IGF-1 has major insulin-like effects on many cell types expressing the IGF-1 receptor, including skeletal muscle, where it stimulates glucose uptake, glycolysis and glycogen synthesis. The differential, receptor-mediated actions of IGF-1 and insulin may relate to the relative affinities of ligands for their respective receptors and the distribution of the receptors. Insulin receptors predominate in hepatocytes and adipocytes, while IGF-1 receptors are expressed mainly in mesenchymal cells, such as fibroblasts and myocytes (Froesch and Zapf, 1985). Therefore, the actions of IGF-1 in muscle may be particularly important in up-regulating muscle insulin sensitivity.

X CONCLUSION

Insulin resistance is controlled by many regulatory actions, which result from interactions with other endocrine hormones. Overall, the review concludes that depends on the physiological state of the body, these hormones exert modulatory or inhibitory effects on either insulin synthesis or secretion. However, additional studies involving recent advances in our understanding of insulin action through receptor sites, its interaction with other hormones, its feed-back mechanisms and enzyme regulation will be necessary

to extend our understanding of the basic mechanisms involved.

REFERENCES

[1] Adashi, E.Y., Hsueh, A.J.W., Yen, S.S.C. 1981. Insulin enhancement of luteinizing hormone and follicle-stimulating hormone release by cultured pituitary cells, Endocrinol. 108: 1441-1449.

[2] Agbecha, A., Usoro, C.A. 2017. Serum testosterone and insulin resistance in type 2 male diabetics attending University of Calabar teaching hospital, J Med Soc. 31: 178-184.

[3] Alonso, A., Gonzalez, C. 2008. Relationship between non-genomic actions of estrogen and insulin resistance. Infect. Disord. Drug. Targets. 8(1): 48-51.

[4] Alonso-Magdalena, P., Ropero, A. B., Cederroth, C. R., Baquie, M., Gauthier, B. R., Nef, S., Stefani, E., Nada, A. 2008. Pancreatic Insulin Content Regulation by the Estrogen Receptor ERα, http://.org/10.1371.

[5] Anisha, A., Gupte, Pownall, H.J., Hamilton, D.J. 2015. Estrogen: An Emerging Regulator of Insulin Action and Mitochondrial Function. J. Diabet. Res. 2015: 1-9.

[6] Barros, R. P. A., Gabbi, C., Morani, A., Warner, M., Gustafsson, J.A.2009. Participation of ERα and ERβ in glucose homeostasis in muscle and white adipose tissue. Am. J. Physiol. Endocrino. Meta. 297(1): 127-133.

[7] Barros, R. P. A., Machado, U. F., Warner, M., Gustafsson, J, A. 2006. Muscle GLUT4 regulation by estrogen receptors ERβ and ERα, Proceed. Nat. Accad. Sci. 103(5); 1605-1608.

[8] Bebakar, W. M., Honour, J.W., Foster, D., Liu, Y. L., Jacobs, H. S. 1990. Regulation of testicular function by insulin and transforming growth factor-β, Steroids 55: 266-269.

[9] Becker, W., Kluge, R., Kantner, T., et al. 2004. Differential hepatic gene expression in a polygenic mouse model with insulin resistance and hyperglycemia: evidence for a combined transcriptional dysregulation of gluconeogenesis and fatty acid synthesis. J. Mol. Endocrinol. 32(1): 195-208.

[10] Biorntorp, H.A. 1992. The effects of cortisol on insulin sensitivity in muscle, Acta. Physiol. Scand. 144(4): 425-431.

[11] Brenta, G. 2011. Why can insulin resistance be a natural consequence of thyroid dysfunction? J. thyroid res. 9.

[12] Burcelin, R., Thorens, B., Glauser, M., Gaillard, R.C., Pralong, F.P. 2003.Gonadotropin-releasing hormone secretion from hypothalamic neurons stimulation by insulin and potentiation by leptin, Endocrinol. 144(10): 4484-4491.

[13] Caro, J.F., Armatruda, J.M., 1982. Glucocorticoid induced insulin resistance, J. Clin. Invest. 69: 866-871.

[14] Chang, L., Chiang, S.H., Saltiel, A.R. 2004. Insulin signaling and the regulation of glucose transport, Mol. Med. 10: 65–71.

[15] Chaudhuri P.K., Chaudhuri B., Patel, N. 1986. Modulation of Estrogen Receptor by Insulin and Its Biologic Significance. Arch Surg. 121(11):1322-1325.

[16] Chubb, S.A., Davis, W.A., Davis, T.M. 2005. Interactions among thyroid function, insulin sensitivity, and serum lipid concentrations: The Fremantle diabetes study. J. Clin. Endocrinol. Metab. 90: 5317–20.

[17] Clegg, D.J., Brown, L. M, Woods, S. C., Benoit, S. C.2006. Gonadal hormones determine sensitivity to central leptin and insulin. Diabetes.55 (4): 978–987.

[18] Clement, K., Viguerie, N., Diehn, M., Alizadeh, A., Barbe, P., Thalamas, C., *et al.* 2002; *In vivo* regulation of human skeletal muscle gene expression by thyroid hormone. Genome Res. 12: 281–91.

[19] Corry, D.B., Tuck, M.L. 2003. The effect of aldosterone on glucose metabolism. Curr. Hypertens. Rep. 5: 106 –109.

[20] Deibert, D. C., Defronzo, R. A. 1980. Epinephrine-induced insulin resistance in man. J Clin Invest. 65(3): 717-721.

[21] Frank, N., Elliott, S.B., Brandt, L.E. 2006. Physical characteristics, blood hormone concentrations, and plasma lipid concentrations in obese insulin resistant horses, J. Am. Vet. Med. Assoc. 228: 1383-1390.

[22] Froesch, E.R, Zapf, J. 1985. Insulin-like growth factors and insulin: comparative aspects. Diabetologia .28: 485-493.

[23] Giacchetti, G., Sechi, L.A., Rilli, S., Carey, R.M. 2005. The rennin-angiotensin-aldosterone system, glucose metabolism and diabetes. Trends Endocrinol. Metab. 16:120 –126.

[24] Gonzalez, A., Alonso, N., Alvarez, F., Diaz, M., Martinez, S., Fernandez., Patterson, A. M. 2000. Role of 17 -estradiol and/or progesterone on insulin sensitivity in the rat: implications during pregnancy. J. Endocrinol. 166, 283–291.

[25] Grillo, M.L., Jacobus, A.P., Scalco, R., Amaral, F., Rodrigues, D.O., Loss, E.S., Wassermann, G F. 2005. Testosterone rapidly stimulates insulin release from isolated pancreatic islets through a non-genomic dependent mechanism. Horm. Metab. Res.37 (11):662-5.

[26] Guo, C., Ricchiuti, V., Lian, B.Q., Yao, T.M., Coutinho, P., Romero, J.R., Li, J., Williams, G.H., Adler, G.K. 2008. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-, and proinflammatory adipokines. Circulation. 117:2253–2261.

[27] Horn, P.A., Mohlig, M., Osterhoff, M., Wolter, S., Hofmann, J., Stocking, C., *et al.* 2000. Effect of estradiol on insulin secreting INS-1 cells overexpressing estrogen receptors Eur. J.Endocrinol. 142: 84–91.

[28] Jones, J.I., Clemmons, D.R. 1995. Insulin-like growth factors and their binding proteins: biological actions. Endocr. Rev. 16: 3-34.

[29] Kahn, A.M., Seidel, C.L, Allen, J.C., O'Neil, R.G., Shelat, H., Song, T. 1993. Insulin reduces contraction and intracellular calcium concentration in vascular smooth muscle, Hyperten. 22: 735–742.

[30] Kalsbeek, S., La Fleur, C., Van Heijningen., Buijs, R. M. 2004. Suprachiasmatic GABAergic inputs to the paraventricular nucleus control plasma glucose concentrations in the rat via sympathetic innervation of the liver, J. Neurosci. 24(35): 7604–7613.

[31] Klieverik, L. P., Janssen, S. F., Van Riel A., *et al*. 2009. "Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver," Proceed. Nat. Acad. Sci. 106(14): 5966–5971.

[32] Kraus, D., Jager, J., Meier, B., Fasshauer, M., Klein, J. 2005. Aldosterone inhibits uncoupling protein-1, induces insulin resistance, and stimulates proinflammatory adipokines in adipocytes. Horm Metab Res. 37: 455– 459.

[33] Kumagai, E., Adachi, H., Jacobs, D.R., Hirai, Y., Enomoto,M., *et al*.2011. Plasma aldosterone levels and development of insulin resistance Prospective Study in a General Population. Hypertension. 58:1043-1048.

[34] Leung, D.W., Spencer, S.A., Cachianes, G., *et al*. 1987.Growth hormone receptor and serum binding protein: purification, cloning and expression. Nature, 330: 537-543.

[35] Lin, T., Vinson, N., Terracio, L. 1986. Characterization of insulin and insulin-like growth factor receptors in purified Leydig cells and their role in steroidogenesis in primary culture: a comparative study. Endocrinol. 119: 1641-1647.

[36] Luther, J.A. 2014. Effects of aldosterone on insulin sensitivity and secretion. Steroids, 54-60.

[37] Mathews, L.S., Hammer, R.E., Brinster, R.L., Palmiter, R.D. 1988. Expression of insulin-like growth factor I in transgenic mice with elevated levels of growth hormone is correlated with growth. Endocrinol. 123: 433-437.

[38] Mauvais-Jarvis, F., Clegg, D. J., Hevener, A. L. 2013. The role of estrogens in control of energy balance and glucose homeostasis, Endocrine Rev. 34(3): 309-338.

[39] Mootha, V .K., Dwyer, A.A., Hardin, M., Eriksson K., Tripathy, D., *et al*., 2005. Relationship between testosterone levels, insulin sensitivity and mitochondrial function in men. Diabet.Care. 28(7): 1636-1642.

[40] Muller-Hess, R., Gesser, C A., Pitter, P., Chappuis, P., Jequier, E., Felber, J P.1975. Interactions of insulin and epinephrine in human metabolism: their influence on carbohydrate and lipid oxidation rate. Diabet. Metab. 1(3): 15-17.

[41] Nieuwenhuizen, A.G., Schuilin, G.A., Liem, S.M., Moes, H., Koiter, T.R., Uilenbroek, J.T. 1999. Progesterone stimulates pancreatic cell proliferation *in vivo*. Eur. J. Endocrinol. 140: 256– 263.

[42] Pitteloud, N., Hardin, M., Dwyer, A.A., Valassi, E., Yialamas, M., Elahi, D., Hayes, F.J. 2005. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J. Cli. Endocrinol. Metab. 90(5): 2636–2641.

[43] Plavinik, F.L, Rodrigues, C.I., Zanella, M.T., Ribeiro, A.B. 1992Hypokalemia, glucose intolerance, and hyperinsulinemia during diuretic therapy. Hypertension. II26 –II29.

[44] Polderman, K.H., Gooren, L.J.G., Asscheman, H., Bakker, A., Heine, R.J. 1994. Induction of insulin resistance by androgens and estrogens. J. Clin. Endocrinol. Metab. 79:265–271.

[45] Qin, B.M., Nagasaki, M., Ren, M., Bajotto, G., Oshida, Y., Sato, Y., 2003. Cinnamon extract (traditional herb) potentiates *in vivo* insulin-regulated glucose utilization *via* enhancing insulin signaling in rats, Diabet. Res. Clin. Pract. 62: 139-148.

[46] Rao, P. M., Kelly, D. M., Jones, T. H. 2013. Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. Nat. Rev. Endocrinol. 9(8): 479-493.

[47] Ribas, V., Drew, B. G., Le, J. A., *et al*. 2011. Myeloid-specific estrogen receptor alpha deficiency impairs metabolic homeostasis and accelerates atherosclerotic lesion development," Proceed. Nat. Acad, Sci. 108(39): 16457–16462.

[48] Ribas, V., Nguyen, M. T. A., Henstridge, D. C., *et al*. 2010. Impaired oxidative metabolism and inflammation are associated with insulin resistance in ERα-deficient mice, Am. J.Physoli.Endocrinol.Metab. 298(2): 304-319.

[49] Sherwin, R. S., Sacca, L. 1984. Effect of epinephrine on glucose metabolism in humans: contribution of the liver. Am. J. Physiol. 247(2): E157-165.

[50] Sowers, J.R., Whaley-Connell, A., Epstein, M. 2009. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. Ann. Intern. Med. 150: 776 –783.

[51] Sperling, M.A. 2006. ATP-sensitive potassium channels: neonatal diabetes mellitus and beyond. N. Engl. J. Med. 355:507–510.

[52] Straub, S.G., Sharp, G. W., Meglasson, M.D., De Souza, C.J. 2001. Progesterone inhibits insulin secretion by a membrane delimited, non-genomic action. Biosci. Rep. 21(5): 653-666.

[53] Treiber, K.H., Hess, T.M., Kronfeld, D.S., Boston, R.C., Geor, R.J., Friere, M., Silva, A. M., Harris, P.A., 2006. Glucose dynamics during exercise: Dietary energy sources affect minimal model parameters in trained Arabian geldings during endurance exercise, Equine Vet. J. Suppl. 36: 631-636.

[54] Tritos, N., Mantzoros, C.S., 1998. Syndromes of severe insulin resistance, J. Clin. Endocrinol. Metab. 83: 3025-3030.
[55] Viguerie, N., Millet, L., Avizou, S., Vidal, H., Larrouy, D., Langin, D., *et al*. 2002. Regulation of human adipocyte gene expression by thyroid hormone. J. Clin. Endocrinol. Metab. 87:630–4.
[56] Vijayan, M.M., Leatherland, J.F. 1992. *In vivo* effects of the steroid analogue RU486 on some aspects of intermediary and thyroid metabolism of brook charr, *Salvelinus fontinalis*, J. Exp. Zool. 263: 265-271.
[57] Wada, T., Ohshima, S., Fujisawa, E., Koya, D., Tsuneki, H., Toshiyasu, S. 2009. Aldosterone inhibits insulin-induced glucose uptake by degradation of insulin receptor substrate (IRS) 1 and IRS2 *via* a reactive oxygen species-mediated pathway in 3T3-L1 adipocytes. Endocrinol. 150:1662–1669.
[58] Weinstein, S.P., O'Boyle, E., Fisher, M., Haber, R.S. 1994. Regulation of GLUT2 glucose transporter expression in liver by thyroid hormone: Evidence for hormonal regulation of the hepatic glucose transport system. Endocrinol. 135:649–54.
[59] Yamada, F., Inoue. S., Saitoh, T., Tanaka, K., Satoh, S., Takamura, Y. 1993. Glucoregulatory hormones in the immobilization stress induced increase of plasma glucose in fasted and fed rats, Endocrinol. 132: 2199-2205.
[60] Yasuda, M., Kitabchi, A.E., 1980. Decreased insulin binding of human erythrocytes after dexamethasone or prednisone ingestion, Diabet. 29: 811-815.

BIOGRAPHY

Dr. Bindulekha D.S has done her Ph.D in Zoology from University of Kerala. Currently working as a Guest Faculty in the Department of Zoology, Christian College, Kattakada, University of Kerala, Thiruvananthapuram, India.