http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS

Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2023.453.457

Review Article
Thyroid Hormones Regulate the Thermoregulatory Mechanisms of the Body: Review

Wessam Mansour Filfilan

Department of Biology, Al-Jamoum University College, Umm al-Qura University, Al-Jamum 25375, Saudi Arabia

Abstract
Thyroid hormones (TH) play a critical role in metabolism, energy balance and thermogenesis. The mechanisms whereby thyroid hormone increases heat production have been analyzed with emphasis in more recent developments. Thyroid hormone increases obligatory thermogenesis as a result of the stimulation of numerous metabolic pathways involved in the development, remodeling and delivery of energy to the tissues. In this section, alterations in primary hyperthyroidism and hypothyroidism will be contrasted with the physiological characteristics of TH-dependent regulation in response to fasting and exposure to cold. The current review will discuss the situation with regard to regional thyroid hormones in the Central Nervous System (CNS) and more specifically, in peripheral cells. When caused by exposure to cold or fasting, local anomalies in the CNS are distinct from peripheral compartments, in contrast to hyperthyroidism and hypothyroidism, which differ when similar changes are observed. Lower hypothalamic TH concentrations are associated with cold exposure, although higher peripheral TH levels. The TH tendency is reversed by fasting. Primary hypothyroidism and hyperthyroidism impair them. The current study aims to trace the various mechanisms used by the thyroid gland to regulate the body's energy production process.

Key words: Thyroid hormone, thermoregulation, body temperature, metabolism, energy production

Citation: Filfilan, W.M., 2023. Thyroid hormones regulate the thermoregulatory mechanisms of the body: Review. Pak. J. Biol. Sci., 26: 453-457.

Corresponding Author: Wessam Mansour Filfilan, Department of Biology, Al-Jamoum University College, Umm al-Qura University, Al-Jamum 25375, Saudi Arabia

Copyright: © 2023 Wessam Mansour Filfilan. This is an open access article distributed under the terms of the creative commons attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Competing Interest: The author has declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Warm-blooded creatures or endotherms, keep their body temperatures constant regardless of their surroundings. Ectotherms or cold-blooded creatures, on the other hand, control their body temperature in response to environmental factors like sunlight or a warm rock surface[1]. A more active metabolism and a worse thermodynamic efficiency are the fundamental causes of endothermy[2]. Given that both sets of processes result in increased body temperature and peripheral heat production at the same time[3-5]. It is possible that THs were a key factor in the evolution of endothermy. As a result, THs are essential for obligatory thermogenesis, or the creation of heat that results as a consequence of metabolic rate[6].

Endothermic animals have evolved facultative or adaptive thermogenesis, which is the creation of heat on demand, to adjust to quickly changing environmental temperatures[7,8]. Shivering is the oldest and most basic reaction to cold, although endothermic species have created non-shivering facultative thermogenesis processes that are more effective and long-lasting. The two primary classes of modern endothermic creatures, birds and mammals, have different facultative thermogenesis sites and mechanisms. Skeletal muscle is the primary site of facultative thermogenesis in birds[9], whereas the BAT is the primary site in mammals[10,11].

The sympathetic nervous system (SNS)-mediated activation of BAT is a central mechanism by which THs are important regulators of thermogenesis[12,13]. However, it is not yet understood whether and how environmental temperature affects such consequences. This has therapeutic implications for the recognition and treatment of THs-related disorders such as hypothyroidism and hyperthyroidism, which are characterized by a preference for cold or a preference for heat, respectively[14]. It is also interesting in terms of evolutionary adaptation to cold and warm habitats[3]. The purpose of this study is to ascertain how ambient temperature affects how TH affects energy balance and thermogenesis mechanisms.

ELEMENTS OF THERMOREGULATION

In homeothermic species, thermal regulation consists of a multitude of mechanisms that meticulously regulate core body temperature to ensure proper metabolic process regulation. Energy-intensive metabolic processes' endogenous, activity-dependent heat production must be matched with heat loss from the body's surface in colder climates. Fur insulation is a crucial strategy for reducing body heat loss[15], although intradermal fat's ability to act as insulation has been questioned, at least in mice[16]. Vasodilation and constriction are crucial mechanisms for controlling body temperature by preventing or conserving heat from being lost by peripheral body parts[17].

Brown adipose tissue (BAT) activation is a characteristic of shivering thermogenesis, According to Celi *et al.*[18], whereas involuntary muscular activity is a characteristic of non-shivering (or adaptive) thermogenesis[19]. Through the use of cold-sensitive thermoreceptors, cutaneous cold sensing primarily stimulates the sympathetic nervous system (SNS)[20]. Then, as described by Cohen and Spiegelman[21], the SNS activates pathways regulated by the 3-adrenergic receptor (ARB3) that speed up lipolysis and the release of free fatty acids (FFA) by raising the noradrenaline release from postganglionic sympathetic fibers.

REGULATION OF THERMOGENESIS BY THYROID HORMONES

Although their function in regulating body temperature has not yet been fully elucidated. The THs' significance in directly promoting energy expenditure has been extensively explored and recorded. Brown adipose tissue (BAT) activation is a characteristic of shivering thermogenesis, according to Cheng *et al.*[19], whereas involuntary muscular activity is a characteristic of non-shivering (or adaptive) thermogenesis[19]. Through the use of cold-sensitive thermoreceptors, cutaneous cold sensing primarily stimulates the sympathetic nervous system (SNS)[20]. Then, as described by Cohen and Spiegelman[21] and Fliers *et al.*[22], the SNS activates pathways regulated by the 3-adrenergic receptor (ARB3) that speed up lipolysis and the release of free fatty acids (FFA) by raising the noradrenaline release from postganglionic sympathetic fibers.

INTERNAL BODY TEMPERATURE AND THYROID HORMONES

The THs may directly affect important metabolically active tissues and hence modify required thermogenesis, as shown in several experimental models of hypothyroidism and hyperthyroidism in both animal models and humans. Although this aspect of thermogenesis can also be controlled by the central nervous system, their main job is to integrate different environmental cues and adjust facultative thermogenesis as needed[23]. Through a sophisticated, multilocular central neural network of temperature-sensitive centers, this control circuit reacts to changes in core body temperature directly as well as indirectly through changes in outer temperature signals detected, for example, by skin temperature sensors.

By activating GABAergic neurons that extend to the dorsomedial DMH and the VMH, direct heating or cooling of the POA affects efferent SNS signaling, which in turn changes thermogenesis[24]. By altering sympathetic tone to the BAT, liver and muscle, activation and inhibition of these neurons significantly lowered or increased core body temperature by about 2°C[25] receptor.

Although UCP1 and TRB expression in BAT are closely connected, TRA is required for thermogenesis to produce an adrenergic response[26]. Visceral body fat increases when TRA1 function is impaired, at least in the form of a TRA P398H mutation. Reduced adaptive thermogenesis, insulin resistance and hyperleptinemia are associated with the study of Johann *et al.*[27], as are decreased lipolysis, insulin sensitivity and hyperleptinemia[28].

HEPATIC EFFECTS MEDIATED BY THYROID HORMONES

Through independent and dependent pathways of the Low-Density Lipoprotein Receptor (LDLR), TH affects the distribution of lipids in the liver. Numerous known TH transporters are expressed in the liver, according to studies done on rats. Large Amino Acid Transporter-1 (LAT1) and DIO1 were also highly upregulated by hyperthyroidism, as were monocarboxylate transporter 10 (MCT10) and LAT1[29]. It's interesting to note that DIO1 has recently been demonstrated to be dramatically downregulated following insulin receptor inactivation in animals, along with a drop in the expression of the gene for Apolipoprotein A1 (Apoa1), which similarly lowers levels of High-Density Lipoprotein cholesterol (HDL)[30]. The pathophysiological alterations seen in metabolic syndrome are thus reflected by this DIO1 regulation and its effect on HDL cholesterol.

EFFECTS OF THYROID HORMONE ON ADIPOSE TISSUE

The primary role of WAT is to store energy, which can be released when needed most, such as during cold stress, starvation, or disease. The importance of WAT as a helpful element in the regulation of energy homeostasis has been established since the discovery of leptin[31]. The SNS activity controls the process of mobilizing the substrate, which is primarily controlled at the cellular level by AT's ARB3-induced lipolysis[32]. It's interesting to note that in humans, WAT from various anatomical regions exhibits varying lipolysis susceptibility, with visceral WAT being more susceptible than subcutaneous WAT[33]. Rats can also exhibit distinct variations in the degree of lipolysis[34].

EFFECTS OF THYROID HORMONE ON GLUCOSE METABOLISM

Recently, studies López *et al.*[35] have examined the effects of TH on glucose metabolism. Much more disputed is the evidence on the direct effects of TH on beta-cell mass, insulin secretion and secretion. In the rat beta-cell line RIN5F, TRA-dependent signaling appears to promote beta-cell proliferation and insulin release is increased both *in vitro* and *in vivo*[36]. *In vivo*, studies following high-dose T3 treatment, however, show increased beta cell apoptosis, which was consistent with studies on these effects, whereas a raised beta-cell mass and hyperinsulinemia were discovered in research on the effects of experimental hypothyroidism during the final weeks of ovine gestation[37]. The data on the direct effects of TH on beta-cell mass, insulin secretion and secretion is far more hotly contested. The rat beta-cell line RIN5F exhibits enhanced insulin release both *in vitro* and *in vivo*, suggesting that TRA-dependent signaling encourages beta-cell proliferation[38]. *In vivo*, studies following high-dose T3 treatment, on the other hand, show increased beta cell apoptosis, which was consistent with studies on these effects[39]. Hyperinsulinemia and stimulated beta-cell mass were found in studies on the impact of experimental hypothyroidism in the last weeks of ovine gestation.

PERIPHERAL BLOOD FLOW AND THYROID HORMONE EFFECTS

The focus of this review does not extend to the significance of TH in maintaining circulatory balance and the heart. They have recently been thoroughly studied for their important role in TRA on heart rate, positive inotropy and cardiac hypertrophy[40]. Recent research has looked at how TH affects vasoconstriction and vasodilation in rodents.

Animals with decreased TRA function exhibit reduced phenylephrine-induced vasoconstriction and acetylcholine-induced vasodilation. As a result, the animal's tail no longer functions as a means of thermoregulation, which has detrimental effects on both cardiovascular health and thermogenesis[41].

CONCLUSION

The primary hyperthyroidism suppresses the release and synthesis of TRH due to increased central thyroid hormone levels. In contrast, it appears that there is a direct peripheral lipolytic drive to provide triglycerides via the

AMPK malonyl-CPT1 pathway, despite the consequent large reduction in TSH secretion. On the other hand, local elevations in TH levels in the VMH inhibit these AMPK-malonly-CPT1-driven actions by triggering sympathetic efferences to the liver and BAT. They cause BAT to start producing heat, which is helped by the T3-dependent transformation of WAT into beige fat. Additionally, it encourages hepatic glucose production. The good impact on metabolism also has positive effects on the cardiovascular system. Direct central activation of AHA parvalbuminergic neurons raises blood pressure. All of these systems will help the body's core temperature rise more quickly. Heat-sensitive neurons in the POA will be stimulated by negative feedback and deactivated via GABAergic projections to the DMH and VMH sympathetic outflow. A range of levels of insulin resistance may develop as a result of TH's direct stimulation of insulin manufacture and secretion, depending on the degree of effect on beta cells, glucose generation and local control. Additional variables that control the fine-tuning of peripheral regulation include deiodinases and leptin, which modulate GLUT expression.

SIGNIFICANCE STATEMENT

Thyroid hormone is long known for its profound effect on body temperature regulation. Patients suffering from hyperthyroidism display elevated body temperature and are sensitive to heat, while hypothyroid patients are cold-sensitive. In the current research, the thermogenic effects of thyroid hormones were discussed. Conclusively, it was clear that primary hyperthyroidism suppresses the release and synthesis of TRH due to increased central thyroid hormone levels. Although a direct peripheral lipolytic drive was activated, a large reduction in TSH secretion was initiated. A local elevations in TH levels in the VMH inhibit these AMPK-malonly-CPT1-driven actions by triggering sympathetic efferences to the liver and BAT, it encourages hepatic glucose production.

REFERENCES

1. Alvarez-Crespo, M., R.I. Csikasz, N. Martínez-Sánchez, C. Diéguez, B. Cannon, J. Nedergaard and M. López, 2016. Essential role of UCP1 modulating the central effects of thyroid hormones on energy balance. Mol. Metab., 5: 271-282.
2. Alexander, C.M., I. Kasza, C.L.E. Yen, S.B. Reeder and D. Hernando *et al*., 2015. Dermal white adipose tissue: A new component of the thermogenic response. J. Lipid Res., 56: 2061-2069.
3. Cannon, B. and J. Nedergaard, 2004. Brown adipose tissue: Function and physiological significance. Physiol. Rev., 84: 277-359.
4. Bianco, A.C. and J.E. Silva, 1988. Cold exposure rapidly induces virtual saturation of brown adipose tissue nuclear T3 receptors. Am. J. Physiol. Endocrinol. Metab., 255: E496-E503.
5. Cannon, B. and J. Nedergaard, 2010. Thyroid hormones: Igniting brown fat via the brain. Nat. Med., 16: 965-967.
6. Bonde, Y., O. Breuer, D. Lütjohann, S. Sjöberg, B. Angelin and M. Rudling, 2014. Thyroid hormone reduces PCSK9 and stimulates bile acid synthesis in human[s]. J. Lipid Res., 55: 2408-2415.
7. Capelli, V., C. Diéguez, J. Mittag and M. López, 2021. Thyroid wars: The rise of central actions. Trends Endocrinol. Metab., 32: 659-671.
8. Capelli, V., C. Grijota-Martínez, N.R.V. Dragano, E. Rial-Pensado and J. Fernø *et al*., 2021. Orally induced hyperthyroidism regulates hypothalamic AMP-activated protein kinase. Nutrients, Vol. 13. 10.3390/nu13124204.
9. Branvold, D.J., D.R. Allred, D.J. Beckstead, H.J. Kim and N. Fillmore *et al*., 2008. Thyroid hormone effects on LKB1, MO25, phospho-AMPK, phospho-CREB, and PGC-1α in rat muscle. J. Appl. Physiol., 105: 1218-1227.
10. Contreras, C., F. Gonzalez, J. Fernø, C. Diéguez, K. Rahmouni, R. Nogueiras and M. López, 2015. The brain and brown fat. Ann. Med., 47: 150-168.
11. de Vries, E.M., L. Eggels, H.C van Beeren, M.T. Ackermans, A. Kalsbeek, E. Fliers and A. Boelen, 2014. Fasting-induced changes in hepatic thyroid hormone metabolism in male rats are independent of autonomic nervous input to the liver. Endocrinology, 155: 5033-5041.
12. Dittner, C., E. Lindsund, B. Cannon and J. Nedergaard, 2019. At thermoneutrality, acute thyroxine-induced thermogenesis and pyrexia are independent of UCP1. Mol. Metab., 25: 20-34.
13. Cabral, A., S. Valdivia, M. Reynaldo, N.E. Cyr, E.A. Nillni and M. Perello, 2012. Short-term cold exposure activates TRH neurons exclusively in the hypothalamic paraventricular nucleus and raphe pallidus. Neurosci. Lett., 518: 86-91.
14. Calvo, R.M. and M.J. Obregon, 2011. Presence and regulation of D1 and D2 deiodinases in rat white adipose tissue. Metabolism, 60: 1207-1210.
15. Cannon, B. and J. Nedergaard, 2011. Nonshivering thermogenesis and its adequate measurement in metabolic studies. J. Exp. Biol., 214: 242-253.
16. Cannon, B. and J. Nedergaard, 2012. Yes, even human brown fat is on fire! J. Clin. Invest., 122: 486-489.
17. Castillo, M., J.A. Hall, M. Correa-Medina, C. Ueta, H.W. Kang, D.E. Cohen and A.C. Bianco, 2011. Disruption of thyroid hormone activation in type 2 deiodinase knockout mice causes obesity with glucose intolerance and liver steatosis only at thermoneutrality. Diabetes, 60: 1082-1089.

18. Celi, F.S., R.J. Brychta, J.D. Linderman, P.W. Butler and A.T. Alberobello *et al*., 2010. Minimal changes in environmental temperature result in a significant increase in energy expenditure and changes in the hormonal homeostasis in healthy adults. Eur. J. Endocrinol., 163: 863-872.
19. Cheng, S.Y., J.L. Leonard and P.J. Davis, 2010. Molecular aspects of thyroid hormone actions. Endocr. Rev., 31: 139-170.
20. Christoffolete, M.A., C.C.G. Linardi, L. de Jesus, K.N. Ebina and S.D. Carvalho *et al*., 2004. Mice with targeted disruption of the Dio2 gene have cold-induced overexpression of the uncoupling protein 1 gene but fail to increase brown adipose tissue lipogenesis and adaptive thermogenesis. Diabetes, 53: 577-584.
21. Cohen, P. and B.M. Spiegelman, 2015. Brown and beige fat: Molecular parts of a thermogenic machine. Diabetes, 64: 2346-2351.
22. Fliers, E., A. Boelen and A.S.P. van Trotsenburg, 2014. Central Regulation of the Hypothalamo-Pituitary-Thyroid (Hpt) Axis. In: Handbook of Clinical Neurology, Fliers, E., M. Korbonits and J.A. Romijn (Eds.), Elsevier, Amsterdam, Netherlands, ISBN: 9780444596024, pp: 127-138.
23. Fliers, E., L.P. Klieverik and A. Kalsbeek, 2010. Novel neural pathways for metabolic effects of thyroid hormone. Trends Endocrinol. Metab., 21: 230-236.
24. Grigg, G., J. Nowack, J.E.P.W. Bicudo, N.C. Bal, H.N. Woodward and R.S. Seymour, 2022. Whole-body endothermy: Ancient, homologous and widespread among the ancestors of mammals, birds and crocodylians. Biol. Rev., 97: 766-801.
25. Herrmann, B., L. Harder, R. Oelkrug, J. Chen and S. Gachkar *et al*., 2020. Central hypothyroidism impairs heart rate stability and prevents thyroid hormone-induced cardiac hypertrophy and pyrexia. Thyroid, 30: 1205-1216.
26. Hulbert, A.J. and P.L. Else, 2004. Basal metabolic rate: History, composition, regulation, and usefulness. Physiol. Biochem. Zool., 77: 869-876.
27. Johann, K., A.L. Cremer, A.W. Fischer, M. Heine and E.R. Pensado *et al*., 2019. Thyroid-hormone-induced browning of white adipose tissue does not contribute to thermogenesis and glucose consumption. Cell Rep., 27: 3385-3400.e3.
28. Kalsbeek, A., E. Bruinstroop, C.X. Yi, L. Klieverik, J. Liu and E. Fliers, 2014. Hormonal Control of Metabolism by the Hypothalamus-Autonomic Nervous System-Liver Axis. In: How Gut and Brain Control Metabolism, Delhanty, P.J.D. and A.J. van der Lely (Eds.), S. Karger AG, Basel, Switzerland, ISBN: 978-3-318-02639-9, pp: 1-28.
29. Kalsbeek, A., E. Bruinstroop, C.X. Yi, L.P. Klieverik, S.E la Fleur and E. Fliers, 2010. Hypothalamic control of energy metabolism via the autonomic nervous system. Ann. New York Acad. Sci., 1212: 114-129.
30. Klieverik, L.P., E. Foppen, M.T. Ackermans, M.J. Serlie and H.P. Sauerwein *et al*., 2009. Central effects of thyronamines on glucose metabolism in rats. J. Endocrinol., 201: 377-386.
31. Klieverik, L.P., S.F. Janssen, A. van Riel, E. Foppen and P.H. Bisschop *et al*., 2009. Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. Proc. Natl. Acad. Sci. U.S.A., 106: 5966-5971.
32. López, M., C.V. Alvarez, R. Nogueiras and C. Diéguez, 2013. Energy balance regulation by thyroid hormones at central level. Trends Mol. Med., 19: 418-427.
33. López, M., 2018. AMPK vars: The VMH strikes back, return of the PVH. Trends Endocrinol. Metab., 29: 135-137.
34. López, M., 2022. Hypothalamic AMPK as a possible target for energy balance-related diseases. Trends Pharmacol. Sci., 43: 546-556.
35. López, M., R. Nogueiras, M. Tena-Sempere and C. Diéguez, 2016. Hypothalamic AMPK: A canonical regulator of whole-body energy balance. Nat. Rev. Endocrinol., 12: 421-432.
36. López, M., L. Varela, M.J. Vázquez, S. Rodríguez-Cuenca and C.R. González *et al*., 2010. Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. Nat. Med., 16: 1001-1008.
37. Zhang, Y., R. Proenca, M. Maffei, M. Barone, L. Leopold and J.M. Friedman, 1994. Positional cloning of the mouse *obese* gene and its human homologue. Nature, 372: 425-432.
38. Zhang, A., D.H. Sieglaff, J.P. York, J.H. Suh and S.D. Ayers *et al*., 2015. Thyroid hormone receptor regulates most genes independently of fibroblast growth factor 21 in liver. J. Endocrinol., 224: 289-301.
39. Zhang, X., Y. Song, M. Feng, X. Zhou and Y. Lu *et al*., 2015. Thyroid-stimulating hormone decreases HMG-CoA reductase phosphorylation via AMP-activated protein kinase in the liver. J. Lipid Res., 56: 963-971.
40. Zhao, Z.D., W.Z. Yang, C. Gao, X. Fu and W. Zhang *et al*., 2017. A hypothalamic circuit that controls body temperature. Proc. Natl. Acad. Sci. U.S.A., 114: 2042-2047.
41. Zhu, X. and S.Y. Cheng, 2010. New insights into regulation of lipid metabolism by thyroid hormone. Curr. Opin. Endocrinol. Diabetes Obesity, 17: 408-413.