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Impact of Thyroxine on collagen dynamics and tissue remodeling in the Common Indian Toad (*Duttaphrynus melanostictus*)

Subhasmita Pattnaik, Gitanjali Mishra, Santhosh Goud
Department of Zoology, Berhampur University, Bhanja Bihar, Odisha, India

Abstract
Collagen is a fibrous protein that contributes as a major structural protein in animal skin and bone connective tissue. Collagen comprises about 30% of the whole body's protein content, especially in mammals. It is found in the bones, blood vessels, cartilage, corneas, dentin of teeth, etc. Fibrous tissues such as the skin, tendons, and ligaments are found as elongated fibrils. It constitutes 1-2% of muscle tissue, a foremost component of the endomysium. The effect of thyroxine (T_4) on collagen characteristics of Skin (Dorsal & Ventral) & Muscle tissue of common Indian toad was investigated in the present study. Thyroxine is essential for both collagen synthesis and matrix metabolism. In the present study, the solubilities of collagen in salt media, salt soluble/insoluble collagen ratio, and % of salt solubility decreased in both dorsal and ventral skin following seven consecutive days of thyroxine administration. Since salt-soluble collagen is regarded as newly synthesized collagen, our results show that the salt solubility of skin and muscle collagens decreased following thyroxine treatment, suggesting that thyroxine decelerates growth by reducing collagen synthesis. The other biochemical parameters like acid soluble, insoluble, total collagen, and acid soluble/insoluble ratio and % of acid solubility increased in both dorsal and ventral skin, except in % acid solubility in ventral skin. A tissue-specific action of thyroid hormone administration in the common Indian toad is shown by the results of muscle tissue where almost all the collagen characteristics decreased though differing to some extent in degree of response. The role of thyroid hormones in controlling the physiological processes clearly shows that the anabolic and catabolic actions depend to a large extent on the dose of the hormone administrated and are species-specific.

Keywords: Thyroxine(T_4), Collagen, Common Indian toad

Introduction

Thyroid hormones (THs), thyroxine (T_4), and triiodothyronine (T_3) play an essential role in the development and metabolism of many tissues and organs and exert profound metabolic effects in adult life, including changes in oxygen consumption, protein, carbohydrate, lipid, and vitamin metabolism (Oliva *et al.*, 2013) [29]. Hormonal production of the thyroid gland is constituted of T_4 (80%) and T_3 (20%). In the circulation, whole T_4 originates from thyroid secretion, but most T_3 (80%) is produced extrathyroidally from T_4 deiodination (Sapin & Schlienger, 2003) 34[]. Thyroid hormones have been reported to modulate cell morphology, differentiation, and proliferation (Lima *et al.*, 1997; Trentin, 1998; Trentin, 2006) [22, 40, 41]. Theoretically, hyperthyroidism may be accompanied by increased soluble and insoluble collagen catabolism. Hypothyroidism seems to be accompanied by decreased rates of catabolism of collagen. (Purnell, *et al*., 1961, Salvi, *et al*., 1996, Diez, *et al*., 2002, Garrity & Bahn, 2006, Magnan *et al*., 2014, Berardi *et al*., 2014) [2, 3, 10, 13, 25, 30, 33].

Collagen is a predominant animal protein, comprising roughly one-third of the total protein content in mammals. It shall consist of 25-30% of the total proteins in vertebrates. The term "collagen" originates from the Greek words 'kolla' and 'genos,' signifying glue and formation, respectively. It possesses a range of biological and pharmacological applications. Their applications encompass pain management for osteoarthritis, hypertension, tissue engineering, human implants, and the control of angiogenic disorders (Rehn *et al*., 2001; Muralidharan, 2013) [27, 31]. Collagen is the major protein in mammals, constituting 30% of total protein mass and accounting for roughly 70% of the dry weight of human skin (Bauer and Uitto, 1979; Rycker *et al*., 1984). The collagen superfamily comprises 29 proteins (Sorushanova, *et al*., 2019) [45] numbered using Roman numerals in vertebrates (I–XXVIII). Collagen XXIX is referred to as epic epidermal collagen (Soderhall *et al*., 2007) [46], but the COL29A1 gene tended to be the same as the COL6A5 gene, and the α1(XXIX) chain corresponded to the α5(VI) chain (Gara *et al*., 2008) [48]. It is predominantly located in skin, cartilage, bone, and tendons, which serves a vital role in structural integrity and functionality. Numerous studies have demonstrated that orally ingested gelatin or collagen hydrolysates confer advantages, including alleviating joint discomfort, enhancing bone density, reducing blood pressure, augmenting the moisture content of the stratum corneum, and regulating the circulatory system (Yamamoto, 2015) [43]. In muscle tissue, it functions as a primary constituent of the endomysium. Collagen comprises one to two percent of muscle tissue and represents six percent of the mass of robust, tendinous muscles (Liu *et al*., 2007) [23]. The fibroblast is the predominant cell responsible for collagen synthesis. Collagenous proteins are regarded not only as a crucial raw material for producing leather, gelatin, and adhesives but are also extensively utilized in manufacturing food products, cosmetics, pharmaceuticals, and human medicine. Moreover, collagen scaffolds may be utilized for military purposes owing to their wound-healing capabilities. (Jafari Sabet, 2016).

Thyroid hormones are documented to enhance collagen and glycosaminoglycan formation; however, the reported results, including the precise types of collagen impacted, vary across the literature. The capacity of thyroxine (T4) to selectively enhance collagen synthesis, in contrast to glycosaminoglycans (GAG), in scaffold-free synthetic cartilage produced from articular chondrocytes (Whitney *et al*., 2017) [42]. Collagen formation was found to be variable but generally slower than the increase in the weight of the thyroid (Harkness, *et al*., 1953) [14].

Objectives

Estimating collagen characteristics following thyroxine (T_4) treatment at a dose of (0.5µg/gm body wt.)

1. Total collagen content
2. Solubility of collagen in dilute salt solutions
3. Solubility of collagen in dilute acid
4. Soluble/insoluble collagen ratio.
5. % of solubility

Materials and Methods

The common Indian toads of both sexes were collected and reared for the present study. They were acclimated in the laboratory condition at room temperature for 3-4 days in wire-netted plastic cages (75*40*35 cm) size containing a moist sand bed. Every day, they were forced-fed with goat liver (composition mg/g wet wt: 110±41 protein, 84±16 lipid, 2.3±1.1 glycogen), and water was provided *ad libitum*. All collected animals were used within five to seven days of collection. The various biochemical parameters were estimated with all the batches of animals of various sizes.

After laboratory acclimation, animals of mixed sexes of different age groups were divided into control and treated groups. The treated group of toads was injected intramuscularly with thyroxine (T_4) and Na salts (Fluka A.G.) at a dose of 0.5µg/gm dissolved in 0.65% NaCl solution, pH 8.3, while the control animals received an equal value of 0.65% NaCl solution, pH 8.3. This injection schedule continued for 7 days. On the 8th day, the animals were sacrificed to estimate biochemical parameters.

Tissue Processing:

Dorsal skin, ventral skin, and Muscle tissues of both control & treated group animals were processed for the extraction and estimation of collagen fractions following the method of Neuman & Logan (1950) [28] as modified by Leach (1960) [21]. A student's t-test was used to evaluate the statistical significance of the data.

Results and Discussion

Thyroxine (T4) administration affected tissue-specific collagen characteristics in the common Indian toad.

1. Dorsal Skin: T4 treatment resulted in a significant decrease in salt-soluble collagen, salt-soluble/salt-insoluble ratio, and percentage of salt solubility ($P<0.001$) compared to controls. There was an insignificant increase in acid-soluble collagen and acid-soluble/insoluble ratio (P, NS), but the percentage of acid solubility increased significantly ($P<0.05$). Insoluble and total collagen content of dorsal skin increased significantly ($P<0.002$ and $P<0.05$, respectively) after T4 treatment (Table 1, Fig. 1 & 2).
2. Ventral Skin: After T4 administration (0.5µg/gm body weight for 7 days), salt-soluble collagen decreased significantly ($P<0.05$), while salt-soluble/salt-insoluble ratio and percentage of salt solubility showed no significant changes (P, NS). Acid-soluble collagen and acid-soluble/insoluble ratio increased insignificantly (P, NS), but the percentage of acid solubility decreased significantly ($P<0.05$). Insoluble and total collagen in ventral skin increased significantly ($P<0.02$) after treatment (Table 2, Fig. 3 & 4).
3. Muscle: In muscle tissue, the effects of T4 were distinct compared to dorsal and ventral skin. Salt-soluble collagen, salt-soluble/salt-insoluble ratio, and percentage of salt solubility decreased significantly ($P<0.02$). Acid-soluble collagen increased insignificantly (P, NS), while acid-soluble/insoluble ratio and percentage of acid solubility increased significantly ($P<0.05$ and $P<0.001$, respectively). Insoluble and total collagen content in muscle decreased significantly ($P<0.001$ and $P<0.02$, respectively) following T4 treatment (Table 3, Fig. 5 & 6).

Collagen is a major structural protein in fibrous tissues such as skin, tendons, and ligaments, primarily synthesized by fibroblasts and other epithelial cells (Lullo *et al*., 2002; Kadler *et al*., 2007; Silvipriya *et al*., 2015) [16, 24, 35]. Thyroid hormones, including thyroxine, significantly influence collagen synthesis and metabolism via thyroid hormone receptors in the skin (Torma, 1993; Ahsan *et al*., 1998; Billoni, 2000) [1, 4]. Thyroxine also regulates glycosaminoglycan (GAG) accumulation, with implications for hypothyroid-related tendon calcification and hyperthyroid conditions like exophthalmos (Diez *et al*., 2002; Garrity & Bahn, 2006; Oliva *et al*., 2013) [10, 13, 29].

Previous studies have shown that thyroxine accelerates the conversion of soluble to insoluble collagen, improving collagen synthesis in arthritic models (Kuberasampath and Bose, 1979) [20]. Thyroxine administration also influences collagen cross-linking, stabilizing the extracellular matrix and contributing to physiological changes during development and aging (Mays *et al*., 1991; Singh *et al*., 2016) [26, 36]. The present study supports these findings, demonstrating that thyroxine decreased salt-soluble collagen in dorsal skin and muscle tissues, suggesting reduced collagen synthesis. Simultaneously, it increased acid-soluble collagen in various tissues, enhancing collagen cross-linking activity. These results further illustrate the tissue-specific responses to thyroxine in the common Indian toad (Klein, 1969; Klein & Rudolph, 1974) [17, 18].

The results emphasize thyroxine's significant role in modulating collagen dynamics—synthesis, degradation, and cross-linking—across different tissues. This study highlights the broader physiological implications of thyroid hormones in regulating connective tissue integrity and function.

Table- 1: Effect of thyroxine (T_4) (0.5µg/gm) on collagen characteristics of Dorsal skin in Common Indian toad. Values for soluble, insoluble and total collagen are mg/gm tissue wet-weight (Mean ± SEM), Numbers in parentheses indicate sample size, NS, Not significant, at 0.05 confidence level.

Experimental condition	SALT SOLUBLE	ACID SOLUBLE	INSOLUBLE	TOTAL	SALT SOLUBLE/SALT INSOLUBLE	ACID SOLUBLE/ ACID INSOLUBLE	% of salt solubility	% acid solubility
Control	34.813	49.616	187.247	276.077	0.190	0.172	15.922	12.376
	±	±	±	±	±	±	±	±
	3.092	2.815	3.259	8.996	0.008	0.009	0.569	0.469
	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
P	P<0.001	P, NS	P<0.002	P<0.05	P<0.001	P, NS	p<0.001	p<0.05
Treated	11.255	66.372	247.064	337.748	0.045	0.227	4.818	17.053
	±	±	±	±	±	±	±	±
	2.054	12.111	16.038	24.440	0.005	0.030	0.538	1.808
	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

Table- 2: Effect of thyroxine (T_4) (0.5µg/gm) on collagen characteristics of Ventral skin in Common Indian toad. Values for soluble, insoluble and total collagen are mg/gm tissue wet-weight (Mean ± SEM), Numbers in parentheses indicate sample size, NS, Not significant, at 0.05 confidence level.

Experimental condition	Salt soluble	Acid soluble	Insoluble	Total	Salt soluble/salt insoluble	Acid soluble/ acid insoluble	% of salt solubility	% acid solubility
Control	48.171	33.747	135.559	239.179	0.189	0.187	17.377	20.346
	±	±	±	±	±	±	±	±
	4.443	3.044	7.729	12.018	0.020	0.019	1.544	1.242
	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
P	P<0.05	P, ns	P<0.02	P<0.02	P, ns	P, ns	P, ns	P<0.05
Treated	33.678	41.514	209.707	324.172	0.207	0.257	17.712	15.624
	±	±	±	±	±	±	±	±
	4.566	3.738	26.513	27.893	0.0296	0.052	1.778	1.569
	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

Table- 3: Effect of thyroxine (T_4) (0.5µg/gm) on collagen characteristics of Muscle in Common Indian toad. Values for soluble, insoluble and total collagen are mg/gm tissue wet-weight (Mean ± SEM), Numbers in parentheses indicate sample size, NS, Not significant, at 0.05 confidence level.

Experimental condition	Salt soluble	Acid soluble	Insoluble	Total	Salt soluble/salt insoluble	Acid soluble/ acid insoluble	% of salt solubility	% acid solubility
Control	28.143	29.851	76.641	170.146	0.176	0.532	16.533	16.832
	±	±	±	±	±	±	±	±
	3.048	3.401	4.604	16.874	0.023	0.102	1.922	2.312
	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
P	P, ns	P, ns	P<0.001	P<0.02	P, ns	P<0.05	P<0.02	P<0.001
Treated	21.330	41.726	39.414	112.163	0.125	0.788	11.088	39.849
	±	±	±	±	±	±	±	±
	2.909	5.617	5.265	12.666	0.008	0.051	0.647	1.555
	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)

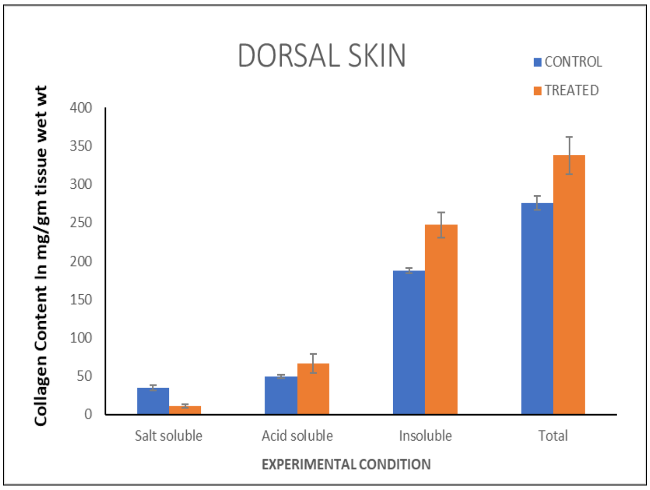

Fig-1: Salt soluble, acid soluble, insoluble & total collagen fraction in dorsal skin of common Indian toad by the administration of T_4 (0.5 µg/gm). Values are mg/gm tissue wet wt., columns represent the mean values & vertical bars SEM.

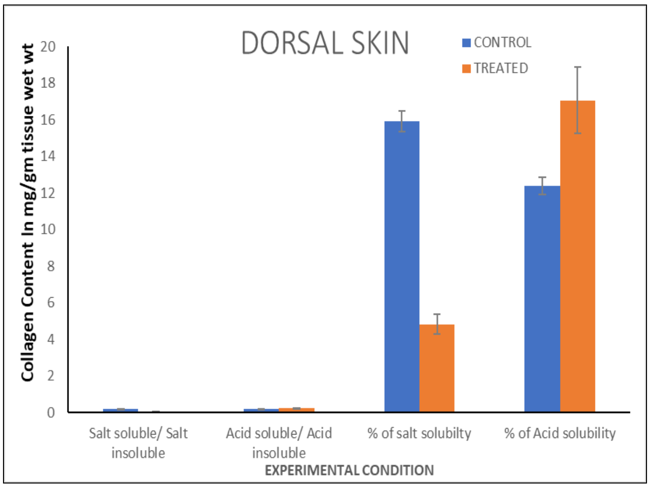

Fig 2: Salt soluble/ salt insoluble, acid soluble/ acid insoluble, % of salt solubility, % of acid solubility collagen fraction in dorsal skin of common Indian toad by the administration of T4 (0.5 µg/gm). Values are mg/gm tissue wet wt., columns represent the mean values & vertical bars SEM.

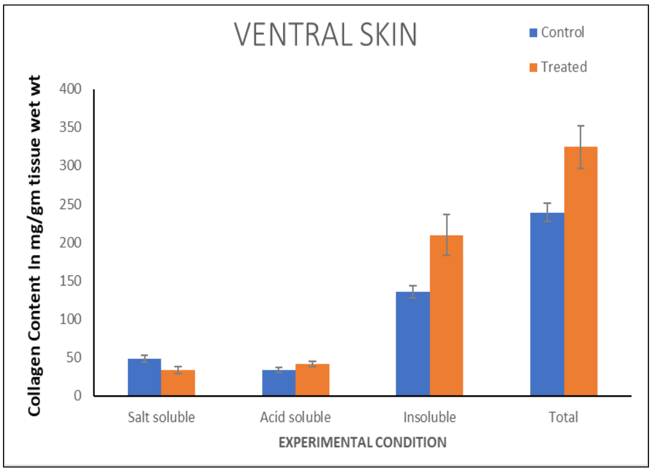

Fig 3: Salt soluble, acid soluble, insoluble & total collagen fraction in ventral skin of common Indian toad by the administration of T4 (0.5 µg/gm). Values are mg/gm tissue wet wt., columns represent the mean values & vertical bars SEM.

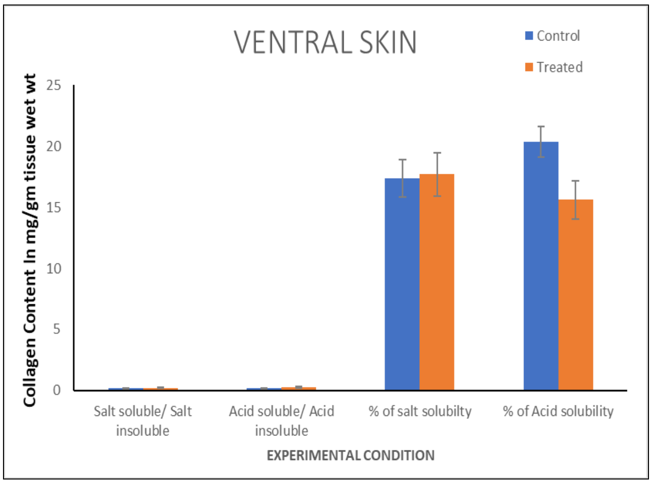

Fig 4: Salt soluble/ salt insoluble, acid soluble/ acid insoluble, % of salt solubility, % of acid solubility collagen fraction in ventral skin of common Indian toad by the administration of T4 (0.5 µg/gm). Values are mg/gm tissue wet wt., columns represent the mean values & vertical bars SEM.

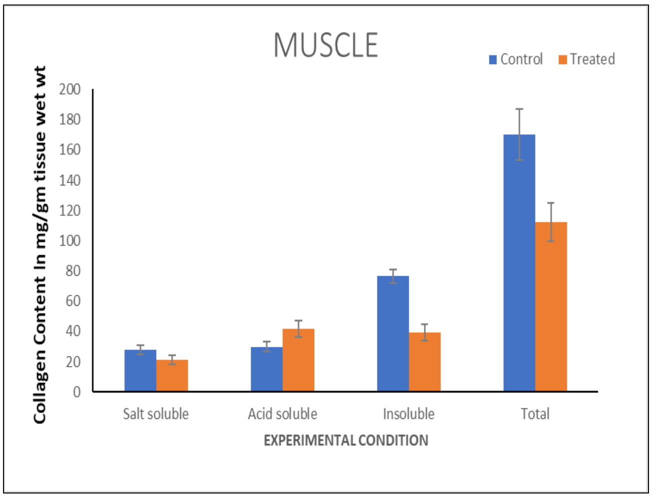

Fig 5: Salt soluble, acid soluble, insoluble & total collagen fraction in muscle of common Indian toad by the administration of T4 (0.5 µg/gm). Values are mg/gm tissue wet wt., columns represent the mean values & vertical bars SEM.

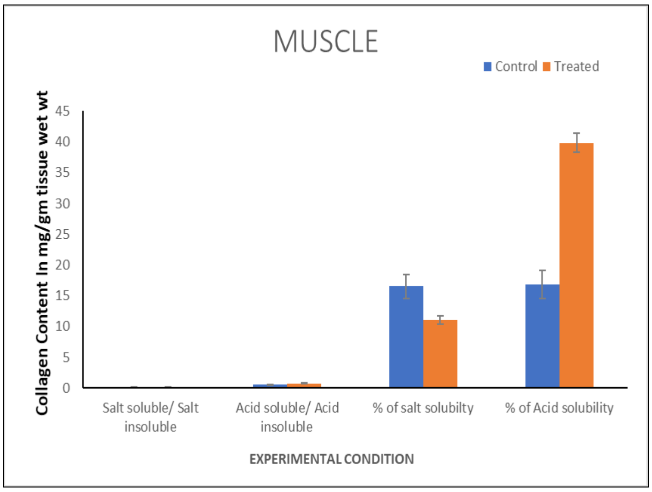

Fig 6: Salt soluble/ salt insoluble, acid soluble/ acid insoluble, % of salt solubility, % of acid solubility collagen fraction in muscle of common Indian toad by the administration of T4 (0.5 µg/gm). Values are mg/gm tissue wet wt., columns represent the mean values & vertical bars SEM.

Conclusion: Thyroxine is crucial for collagen synthesis and matrix metabolism, and its effects on collagen characteristics are influenced by various factors (Timiras, 1972) [37]. The formation of intermolecular cross-links in collagen affects tissue stability and physiological function (Kohn, 1978) [19]. The present study demonstrates that thyroxine administration enhances collagen synthesis, accelerates the conversion of soluble to insoluble collagen, and exhibits tissue-specific effects in the common Indian toad. These findings provide insights into thyroxine's role in collagen remodeling and its potential therapeutic implications in connective tissue disorders.

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