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Adrenergic regulation of the thyroid Axis: β- and α-Adrenergic signals as drivers of hormonal and metabolic homeostasis in lizard *Podarcis siculus*

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ABSTRACT

The adrenergic system is known for its ability to influence various physiological and metabolic processes; however, its involvement in thyroid function in non-mammalian vertebrates remains poorly explored. Adult male lizards were treated with β-adrenergic agonists (isoproterenol, terbutaline, and L-isopropylamino-3-(2-thiazoloxy)-2-propanol) and the α-adrenergic antagonist (phentolamine). The effects of β-adrenergic agonists and the α-adrenergic antagonist administered as single and repeated injections were evaluated on plasma TSH, thyroid hormones, hepatic 5′-T_4 ORD (type II monodeiodinase) activity, hepatic thyroid hormone contents, blood glucose levels, and thyroid gland histology. β-adrenergic stimulation produced a dose-dependent decrease in plasma TSH, accompanied by significant increases in circulating T_3 and T_4 levels. These changes were associated with enhanced hepatic monodeiodinase activity, increased hepatic T_3 content, reduced hepatic T_4 levels, and histological features indicative of thyroid activation. Repeated administrations amplified these effects. In contrast, phentolamine treatment increased plasma TSH levels but reduced circulating and hepatic T_3, increased hepatic T_4, and tended to decrease deiodinase activity, indicating impaired peripheral thyroid hormone activation. Histological analysis showed reduced follicular synthetic activity, although colloid resorption vacuoles were still present. IPT treatment produced no significant effects. All treatments induced hyperglycaemia, with stronger responses after repeated administrations, suggesting coordinated regulation of thyroid function and energy metabolism by adrenergic pathways. The results demonstrate that β-adrenergic signaling promotes thyroid activation and peripheral hormone conversion, whereas α-adrenergic blockade disrupts thyroid hormone homeostasis. These findings highlight a key role of adrenergic mechanisms in the neuroendocrine and metabolic regulation of reptiles, supporting their importance in physiological adaptation to environmental variability.

1. Introduction

The adrenergic system is a fundamental component of vertebrate neuroendocrine regulation, playing a central role in the maintenance of physiological homeostasis through the action of catecholamines released by sympathetic nerve terminals and the adrenal medulla (Ozdemir, 2024). These effects are mediated by adrenergic receptors, G protein-coupled receptors (GPCRs) classified into α and β subfamilies, which differ in pharmacological and functional properties (Bylund, 2013). Subtype diversity (α_1, α_2, β_1, β_2, β_3) underlies tissue-specific responses, including modulation of cardiovascular function, metabolism, and endocrine activity (Abosamak et al., 2026).

Beyond their classical roles, adrenergic receptors are widely distributed in the central nervous system and neuroendocrine tissues, including hypothalamic nuclei and the pituitary gland, suggesting involvement in the regulation of hypothalamic–pituitary axes. In particular, β-adrenergic receptors have been implicated in the modulation of neuroendocrine outputs, with evidence of species-specific differences in receptor distribution within brain regions such as the hippocampus and hypothalamus (De Souza, 1985; Duncan et al., 1991;

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Little et al., 1992). These findings support a conserved but plastic role of adrenergic signaling in vertebrate endocrine integration.

Adrenergic modulation of thyroid function has been demonstrated primarily in mammalian models, where β-adrenergic stimulation influences iodide uptake and thyroid activity, largely *via* β_2 receptor activation in follicular cells (Melander et al., 1975). Conversely, α-adrenergic pathways have been associated with modulation of thyroid hormone secretion through interactions with TSH-dependent mechanisms (Ahrén, 1985). Despite these observations, most available evidence derives from mammalian systems, and the evolutionary conservation of adrenergic control of thyroid physiology remains poorly understood.

Although the interaction between the autonomic nervous system and thyroid function is well documented in endotherms, a systematic review of the scientific literature on lower vertebrates reveals that research on adrenergic-thyroid interaction has been limited to specific functional niches, leaving significant gaps at the morphofunctional level. In teleost fish, research has almost exclusively centered on how catecholamines modulate peripheral deiodinase pathways and tissue-specific T_3/T_4 clearance during environmental stress (Maciag et al., 2023). In amphibians, studies have primarily investigated the indirect, central synergistic role of adrenergic signaling on the HPT axis specifically to accelerate TSH-dependent development during metamorphosis (Köhrle and Frädrich, 2022; Hanada et al., 2023). In birds, sympathetic innervation directly influences follicular secretory activity during seasonal acclimatization and thermoregulation (Little, 2021; Janovska et al., 2023).

However, despite these well-documented interactions in other ectothermic and endothermic lineages, detailed morphofunctional evidence regarding the direct, acute effects of selective adrenergic agonists and antagonists on thyroid morphophysiology remains remarkably limited in reptiles, particularly in lizards.

Reptiles represent a valuable comparative model for investigating endocrine evolution, as their hypothalamic–pituitary–thyroid (HPT) axis shares fundamental organizational and functional features with that of mammals. In particular, the lizard *Podarcis siculus*, widely distributed in Southern Europe, has emerged as a useful model for endocrine and metabolic studies due to its well-characterized thyroid physiology and ecological adaptability (Sciarrillo et al., 2000, 2025). However, the role of adrenergic signaling in regulating thyroid hormone metabolism in squamate reptiles remains largely unexplored. To address this gap, Sciarrillo et al. (2025) have recently demonstrated that the catecholaminergic system (adrenaline, noradrenaline, and dopamine) exerts precise and differentiated control over the HPT axis of the lizard *Podarcis siculus*. These findings confirm that the mechanisms of central nervous system regulation of the thyroid are phylogenetically ancient and highly conserved.

The present study investigates the effects of adrenergic modulation on thyroid hormone metabolism in lizard *Podarcis siculus*, with emphasis on both central and peripheral regulatory levels. Pharmacological activation and inhibition of adrenergic pathways were achieved using selective β-adrenergic agonists (isoproterenol, terbutaline, and L-isopropylamino-3-(2-thiazoloxy)-2-propanol) and the α-adrenergic antagonist phentolamine. Endocrine responses were assessed by evaluating circulating thyroid-stimulating hormone (TSH), thyroxine (T_4), and triiodothyronine (T_3), as well as hepatic thyroid hormone content and type II 5′-monodeiodinase activity. In addition, thyroid gland histopathology was analyzed to identify morphological correlates of adrenergic modulation.

2. Materials and methods

2.1. Animals and experimental procedures

Animal experiments were performed according to the ethical provisions imposed by the European Union, permitted by the National Committee of the Italian Ministry of Health on *in vivo* experimentation and organized to minimize the number of animals used (Sciarrillo et al., 2025).

Sexually mature male specimens of the *Podarcis siculus* lizard were captured in Campania, specifically in the area near the Metropolitan City of Naples – which has the highest population density in Europe – between November and December, when the thyroid gland is in a state of winter dormancy and, consequently, its activity is inhibited.

Then, we selected fifty lizards without significant differences in body mass and placed them in large soil-filled terraria containing heather and indoor subjected to photoperiod (11 h of daylight) and natural temperature (15–24 °C); moreover, they were daily fed honeycomb moth (*Galleria mellonella*) caterpillars, water was available *ad libitum* and to reverse capture-related stress conditions, an acclimatization period of 15 days was allowed before starting the treatment (Sciarrillo et al., 2025).

All the lizards used for analysis were about the same age and were weighed on a precision balance before and after the experimental tests. The animals were sacrificed by decapitation after deep anaesthesia with ketamine hydrochloride (Parke-Davis, Berlin, Germany) 325 mg/kg of body weight (Sciarrillo et al., 2025).

The lizards were treated with four different substances: isoproterenol (IPNE) (Sigma Chemical Co., St. Louis, USA), a non-selective β-adrenergic receptor agonist; Terbutaline (Terb) (Sigma Chemical Co., St. Louis, USA), a selective β_2-adrenergic receptor agonist; L-isopropylamino-3-(2-thiazoloxy)-2-propanol (ITP) (Sigma Chemical Co., St. Louis, USA), a selective β_1-adrenergic receptor agonist; and Phentolamine (PHA) (Sigma Chemical Co., St. Louis, USA), a non-selective competitive α-adrenergic receptor antagonist. All substances were dissolved and diluted in 0.7% NaCl immediately prior to the experiment.

Experimental substances were administered *via* intraperitoneally (ip) injection in a standardized vehicle volume of 0.10 mL (100 μL) of sterile 0.7% NaCl saline. General anaesthesia was induced *via* ip. injection of Ketamine hydrochloride (325 mg/kg). To ensure volumetric accuracy for lizards weighing 15–20 g, the stock solution was diluted 1:2 in sterile saline (working concentration: 50 mg/mL), resulting in a final injection volume of 0.10–0.13 mL per animal. Thermal support (30 °C ± 1 °C) was provided throughout the procedure to optimize recovery.

Doses for IPNE, Terb, ITP and PHA were adapted from mammalian pharmacological profiles (Melander et al., 1975) and adjusted for ectothermic models. Because definitive dose-response curves for these specific adrenergic agents are unavailable for this reptile species, and establishing them was restricted by wildlife conservation ethical constraints, saturating doses were deliberately selected. In ecophysiological protocols involving ectotherms, utilizing robust, functionally maximal doses is required to ensure complete receptor engagement and account for the lower metabolic rates, delayed clearance, and potential differences in receptor affinity characteristic of reptiles compared to endothermic models. This saturation approach ensures that non-significant results reflect a true lack of detectable downstream physiological response rather than sub-threshold receptor activation.

The 2-h post-injection time point for animal sacrifice was selected based on comparative pharmacological and ecophysiological criteria. Because baseline plasma half-life ($t_{1/2}$) data for IPNE, Terb, ITP and PHA are currently unavailable for reptiles, the sampling window was extrapolated by adjusting standard mammalian baselines (where these compounds present short elimination half-lives, ranging from minutes to a few hours) to account for the significantly lower metabolic and clearance rates characteristic of ectotherms. Furthermore, this 2-h latency ensures sufficient time for downstream biochemical cascades to develop and stabilize in the target tissues, representing a pharmacodynamic plateau rather than an arbitrary choice.

For animals received a repeated injection protocol (Groups V–VIII), consisting of three consecutive doses administered at strict 24-h intervals, every morning at 08:00 AM for three consecutive days. This fixed schedule was maintained to reduce any potential variance driven

by circadian physiological fluctuations. The third and final injection was administered on the morning of the last day, exactly 2 h before the animals were sacrificed.

The animals were divided into eight groups ($n = 5$), according to the following scheme:

CONTROL GROUP I: lizards ($n = 5$) that received an injection of 0.7% NaCl and were sacrificed 2 h after the last injection.

CONTROL GROUP II: lizards ($n = 5$) that received three injections of 0.7% NaCl and were sacrificed 2 h after the last injection.

GROUP I: lizards ($n = 5$) that received an injection of 0.05 μmol of IPNE and were sacrificed 2 h after the last injection.

GROUP II: lizards ($n = 5$) that received an injection of 0.5 μmol of Terb and were sacrificed 2 h after the last injection.

GROUP III: lizards ($n = 5$) that received an injection of 0.5 μmol of ITP and were sacrificed 2 h after the last injection.

GROUP IV: lizards (n = 5) that received an injection of 1.42 μmol of PHA and were sacrificed 2 h after the last injection.

GROUP V: lizards (n = 5) that received three injections of 0.05 μmol of IPNE and were sacrificed 2 h after the last injection.

GROUP VI: lizards (n = 5) that received three injections of 0.5 μmol of Terb and were sacrificed 2 h after the last injection.

GROUP VII: lizards (n = 5) that received three injections of 0.5 μmol of ITP and were sacrificed 2 h after the last injection.

GROUP VIII: lizards (n = 5) that received three injections of 1.42 μmol of PHA and were sacrificed 2 h after the last injection.

Terminal blood samples were collected *via* cardiac puncture under deep Ketamine hydrochloride anaesthesia immediately prior to decapitation. To prevent coagulation and avoid reptile-specific erythrocyte hemolysis, blood was collected using 1 mL syringes pre-coated with lithium heparin. Whole blood was immediately transferred to microcentrifuge tubes, kept on ice, and centrifuged at 3000 ×*g* for 10 min at 4 °C. The isolated plasma was stored at −80 °C until subsequent assays.

2.2. Biochemical analysis

2.2.1. Plasma TSH (thyroid stimulating hormone) and thyroid hormones assays

TSH levels were analyzed using an immunoradiometric assay (IRMA); the serum sample and standards were transferred to tubes coated with anti-ligand antibodies (Sciarrillo et al., 2024, 2025) Subsequently, the tracer/capture reagent, consisting of a mixture of rabbit anti-TSH antibody labelled with ligand and I^{125}(10 pCi), was added to each tube; a cubic spline function was used for the calculations, with the zero standard as one of the standard points. The minimum detectable concentration was 0.01 μIU/ml with an accuracy close to 100% and a mean intra-assay and inter-assay variance of 5.0% and 7.5% respectively. Cross-reactivity studies were performed using substances that, in theory, could interfere with the test's performance. The cross-reactivity of FSH, hCG and LH in the TSH IRMA was found to be negligible (<0.001), which is why it was not included in the analysis of the results (Sciarrillo et al., 2024, 2025).

Plasma T_3 and T_4 concentrations were measured by radioimmunoassay (RIA) using commercial kits (Byk-Sangtec Diagnostica, Dietzenbach, Germany), according to Sciarrillo et al. (2024, 2025).

For T_3 determination, serum samples and standards were incubated in tubes coated with anti-T3 rabbit antibody, in the presence of a tracer amount of [^{125}I]-T_3 (165 kBq) and a blocking buffer (Tris-buffered saline containing 4 mM ANS, 6 mM sodium salicylate, and 0.2% sodium azide; Sigma Chemical Co., St. Louis, USA) to dissociate hormone–protein complexes. The assay sensitivity was 0.1 ng/mL, with an accuracy of approximately 97%. Intra-assay variability ranged from 1.0 to 2.6% ($n = 20$), and inter-assay variability from 3.9 to 5.7% ($n = 12$) (Sciarrillo et al., 2000, 2024, 2025).

T_4 levels were measured following the same procedure, using tubes coated with anti-T4 rabbit antibody and [^{125}I]-T_4 (165 kBq). The assay sensitivity was 0.45 ng/mL, with an accuracy close to 100%. Mean intra- and inter-assay coefficients of variation were 4.6% and 4.3%, respectively. Cross-reactivity was negligible and therefore not considered in data analysis (T_4 in T_3 assay: 1.3%; T_3 in T_4 assay: 0.1%) (Sciarrillo et al., 2000, 2024, 2025).

2.2.2. Hepatic thyroid hormones and 5′ORD (Type II) monodeiodinase

Liver samples were collected and washed in a buffer solution containing MOPS and EDTA at pH 7.4. The concentrations of T_3 and T_4 in liver tissue were measured using a radioimmunoassay (RIA) and expressed as ng per mg of fresh tissue (Sciarrillo et al., 2000, 2024, 2025). Enzymatic activity was reported in pM of T_3 per gram of liver per hour (Sciarrillo et al., 2000, 2024, 2025).

2.2.3. Blood glucose levels

Blood glucose levels were measured by an enzymatic method (Hypocount GA, Amplifon).

2.3. Histological analysis

The thyroid glands were removed and fixed in Bouin's solution and prepared for examination under an optical microscope. Serial sections of the paraffin-embedded samples, 7 μm thick, were subsequently stained using the Galgano stain and examined using a Zeiss Axioskop microscope (Milan, Italy). Height of the follicular cells (μm) and Follicular diameter (μm) were performed on the middle section of three consecutive serial sections to ensure anatomical depth standardization across all samples, in both control and treated samples, using a digital image analysis system (KS 300) (Sciarrillo et al., 2000, 2024, 2025).

To complement the morphometric analysis, a semi-quantitative scoring system was used to evaluate the density of colloid resorption vacuoles. For each animal, 30 follicles were randomly selected and scored on a scale from 0 to 3 by an observer blinded to the treatment groups, according to the following criteria: Score 0 = absent or rare vacuoles (<1–2 per follicle); Score 1 = mild presence, involving less than 25% of the follicular perimeter; Score 2 = moderate presence, with clear colloid erosion involving 25–50% of the perimeter; Score 3 = marked presence, with numerous and confluent vacuoles involving more than 50% of the follicular perimeter.

2.4. Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM). The normality of data distribution within each experimental group was verified using the Shapiro-Wilk test, confirming suitability for parametric analysis ($p > 0.05$). To evaluate the effects of the independent variables (compound type and dose frequency), as well as their potential interaction, data were analyzed using a Two-Way Analysis of Variance (ANOVA), followed by Bonferroni's post-hoc test for multiple comparisons. The threshold for statistical significance was set *a priori* at $p < 0.05$. In all figures and tables, specific significance levels achieved are indicated as follows: $p < 0.05$, $*p < 0.01$, and $**p < 0.001$. All statistical operations were performed using GraphPad Prism (GraphPad Software, La Jolla, CA, USA) (Sciarrillo et al., 2024, 2025).

3. Results

3.1. Effect of β-adrenergic agonists and the α-adrenergic antagonist on plasma TSH levels

β-adrenergic agonists, administered either as a single injection or in three injections with sampling after 2 h, induced changes in plasma TSH levels, indicating a direct and central effect on the pituitary gland and a clearly dose-dependent effect. Circulating TSH levels showed a slight decrease in lizards receiving a single injection of the substances (Fig. 1A), whereas the most pronounced reduction was observed after administration of three doses (Fig. 1B). In particular, lizards that

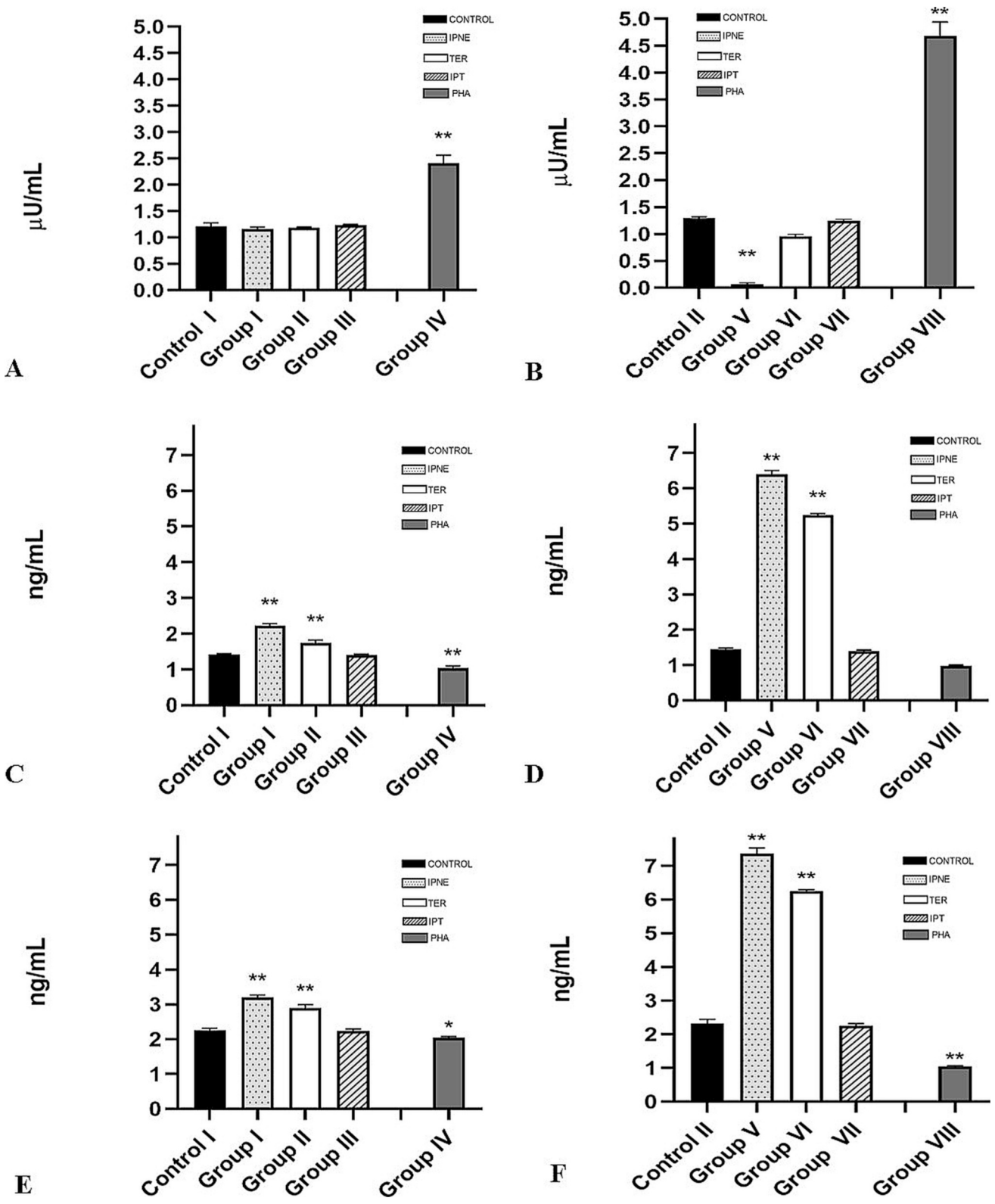

Fig. 1. Plasma TSH (A), T_3 (C), and T_4 (E) levels in *Podarcis siculus* subjected to a single intraperitoneally injections of IPNE (Group I), Terb (Group II), IPT (Group III) and PHA (Group IV) and sacrificed 2 h after the last injection. Plasma TSH (B), T_3 (D), and T_4 (F) levels in *Podarcis siculus* subjected to 3 intraperitoneally injections of IPNE (Group V), Terb (Group VI), IPT (Group VII) and PHA (Group VIII) and sacrificed 2 h after the last injection ($p < 0.05$, *$p < 0.01$, **$p < 0.001$, in the comparison with the different controls). A more detailed description is in the text (see Materials and methods section).

received three injections of IPNE (Group V) showed a marked decrease in plasma TSH levels compared with the control group (TSH: 0.064 ± 0.02 *vs* 1.29 ± 0.03 μUI/mL). Similarly, lizards treated with Terb (Group VI) also exhibited reduced plasma TSH levels (TSH: 0.95 ± 0.02 *vs* 1.29 ± 0.03 μUI/mL). In contrast, animals treated with three injections of ITP (Group VII) showed plasma TSH values very similar to those of the controls (TSH: 1.24 ± 0.03 *vs* 1.29 ± 0.03 μUI/mL) (Fig. 1B).

In contrast, the α-adrenergic antagonist, PHA exerted a stimulatory effect on TSH secretion. A single injection (Group IV) significantly increased plasma TSH levels compared with controls (2.41 ± 0.15 *vs* 1.21 ± 0.06 μUI/mL) (Fig. 1A), while three injections (Group VIII) induced an even greater increase (4.67 ± 0.26 *vs* 1.29 ± 0.02 μUI/mL) (Fig. 1B). These results highlight distinct treatment- and dose-dependent effects of adrenergic modulation on pituitary TSH secretion, suggesting that activation of β-adrenergic pathways exerts an inhibitory influence on TSH release, whereas blockade of α-adrenergic receptors enhances pituitary thyrotropic activity. Moreover, the more pronounced response observed after repeated administrations indicates that prolonged adrenergic stimulation or inhibition may progressively alter the regulatory mechanisms controlling thyroid axis function. Overall, these findings support the involvement of adrenergic signaling in the neuroendocrine regulation of TSH secretion in lizards.

3.2. Effect of β-adrenergic agonists and α-adrenergic antagonist on plasma levels of the thyroid hormones T_3 and T_4

Plasma levels of the thyroid hormones T_3 and T_4 were elevated following treatment with β-adrenergic agonists, both after a single dose and after three consecutive doses. Animals treated with a single dose of IPNE (Group I) showed increased hormone levels compared with the control group (T_3: 2.22 ± 0.05 *vs* 1.42 ± 0.02 ng/mL (Fig. 1C); T_4: 3.20 ± 0.06 *vs* 2.25 ± 0.05 ng/mL (Fig. 1E)). Similarly, lizards that received a single injection of Terb (Group II) also exhibited elevated plasma hormone levels (T_3: 1.73 ± 0.08 *vs* 1.42 ± 0.02 ng/mL (Fig. 1C); T_4: 2.90 ± 1.00 *vs* 2.25 ± 0.05 ng/mL (Fig. 1E)). In contrast, lizards treated with a single injection of IPT did not show significant changes in plasma thyroid hormone levels, which remained comparable to those of the control animals (T_3: 1.40 ± 0.02 *vs* 1.42 ± 0.02 ng/mL (Fig. 1C); T_4: 2.24 ± 1.00 *vs* 2.25 ± 0.05 ng/mL(Fig. 1E)).

The same trend was observed in lizards that received three consecutive administrations of the substances. Specifically, specimens treated with three injections of IPNE (Group V) showed a marked increase in thyroid hormone levels compared with the control group (T_3: 6.40 ± 0.10 *vs* 1.44 ± 0.04 ng/mL(Fig. 1D); T_4: 7.35 ± 0.17 *vs* 2.31 ± 0.12 ng/mL (Fig. 1F)). Likewise, animals treated with three injections of Terb (Group VI) exhibited significantly elevated plasma T_3 and T_4 levels relative to controls (T_3: 5.24 ± 0.05 *vs* 1.44 ± 0.04 ng/mL (Fig. 1D); T_4: 6.24 ± 0.04 *vs* 2.31 ± 0.12 ng/mL (Fig. 1F). In contrast, lizards treated with three injections of IPT (Group VII) displayed plasma T_3 and T_4 values comparable to those observed in the control group (Fig. 1F).

In contrast, circulating plasma levels of the thyroid hormones T_3 and T_4 decreased following both a single administration and three consecutive administrations of PHA in lizard specimens, compared with the control group. In particular, animals treated with a single injection of PHA (Group IV) exhibited reduced plasma levels of T_3 and T_4 relative to controls (T_3: 1.04 ± 0.05 *vs* 1.42 ± 0.019 ng/mL (Fig. 1C); T_4: 2.05 ± 0.02 *vs* 2.25 ± 0.05 ng/mL (Fig. 1E)). An even more pronounced decrease was observed in lizards receiving three consecutive administrations of the substance (Group VIII) (T_3: 0.97 ± 0.03 *vs* 1.44 ± 0.04 ng/mL (Fig. 1D); T_4: 1.03 ± 0.03 *vs* 2.31 ± 0.12 ng/mL (Fig. 1F)).

Overall, these findings indicate that β-adrenergic stimulation promotes thyroid activity, leading to increased circulating levels of T_3 and T_4, whereas α-adrenergic blockade with phentolamine exerts an inhibitory effect on thyroid hormone secretion. The stronger hormonal responses observed after repeated administrations suggest a cumulative or sustained action of adrenergic signaling on thyroid gland function. Furthermore, the absence of significant changes following IPT treatment indicates that not all adrenergic compounds equally affect thyroid endocrine activity. Taken together, these results support a key role of adrenergic mechanisms in the regulation of thyroid hormone secretion in lizards and suggest the existence of differential receptor-mediated pathways controlling thyroid axis responsiveness.

3.3. Effect of β-adrenergic agonists and α-adrenergic antagonist on hepatic thyroid hormones content and 5-T4 ORD (type II) monodeiodinase activity (MDA)

β-adrenergic agonists were also able to modulate the activity of 5′-T_4 ORD (type II monodeiodinase) in liver cells. As shown in Fig. 2A-B, a significant increase in enzyme activity was observed after both a single administration and following three consecutive treatments. In particular, lizards treated with a single injection of IPNE (Group I) showed increased enzymatic activity compared with the control group (3.41 ± 0.15 *vs* 3.05 ± 0.11 pM T_3/g/h) (Fig. 2A). An even more pronounced increase was detected in animals receiving three injections of IPNE (Group V) relative to controls (4.32 ± 0.17 *vs* 3.11 ± 0.09 pM T_3/g/h) (Fig. 2B), as well as in specimens treated with three injections of Terb (Group VI) (4.18 ± 0.13 *vs* 3.11 ± 0.99 pM T_3/g/h) (Fig. 2B). In contrast, IPT treatment, administered either as a single dose or in three consecutive injections, did not produce any significant variation in enzymatic activity compared with the control group (Fig. 2A,B), confirming its lack of effect on hepatic deiodinase function under the experimental conditions tested.

Hepatic T_3 content was higher than in the control group in both the samples that received a single injection and those that received three injections (Fig. 2C-D). Specifically, samples that received a single injection of IPNE (Group I) and samples that received a single injection of Terb (Group II) showed increased hepatic T_3 levels compared with the control (Group I: 4.00 ± 0.17 *vs* 3.15 ± 0.16 ng/mg; Group II: 3.96 ± 0.17 *vs* 3.15 ± 0.16 ng/mg) (Fig. 2C). A more significant increase was observed following treatment of the samples with 3 injections of IPNE (Group V) compared to the control group (4.85 ± 0.22 *vs* 3.89 ± 0.14 ng/mg), and in samples that received three injections of Terb (Group VI). (4.25 ± 0.25 *vs* 3.89 ± 0.14 ng/mg) (Fig. 2D). In contrast, IPT treatment either administered as a single dose or in three consecutive injections, did not produce any significant variation in hepatic T_3 content compared with the control group (Fig. 2C, D).

Conversely, hepatic T_4 content decreased both after a single injection of β-adrenergic agonists and following three consecutive administrations. In particular, animals receiving a single dose of IPNE (Group I) and Terb (Group II) showed reduced hepatic T_4 levels compared with the control group (Group I: T_4: 1.11 ± 0.09 *vs* 1.23 ± 0.13 ng/mg; Group II: 1.06 ± 0.09 *vs* 1.23 ± 0.13 ng/mg) (Fig. 2E, F). A similar decrease was observed after three administrations of IPNE (Group V) and Terb (Group VI), with values lower than controls (Group V: 0.95 ± 0.08 *vs* 1.12 ± 0.11 ng/mg; Group VI: 1.01 ± 0.07 *vs* 1.12 ± 0.11 ng/mg) (Fig. 2E,F). In contrast, IPT treatment, administered either as a single dose or in three consecutive injections, did not produce any significant variation in hepatic T_4 content compared with the control group, indicating a lack of effect on hepatic thyroid hormone availability under the experimental conditions (Fig. 2E, F).

The α-adrenergic antagonist PHA was found to inhibit the activity of 5′-T_4 ORD (type II monodeiodinase) in liver cells. Samples receiving either a single injection of PHA (Group IV) (Fig. 2A) and three injections (Group VIII) (Fig. 2B) showed a reduction in MDA activity compared with controls, although this decrease was not statistically significant.

Hepatic T_3 content was instead significantly reduced following PHA treatment. In particular, animals receiving a single injection (Group IV) showed lower hepatic T_3 levels compared with the control group (3.13 ± 0.15 *vs* 3.5 ± 0.16 ng/mg) (Fig. 2C), and a further significant reduction was observed in animals subjected to three injections (Group VIII) (3.01 ± 0.09 *vs* 3.89 ± 0.14 ng/mg) (Fig. 2D).

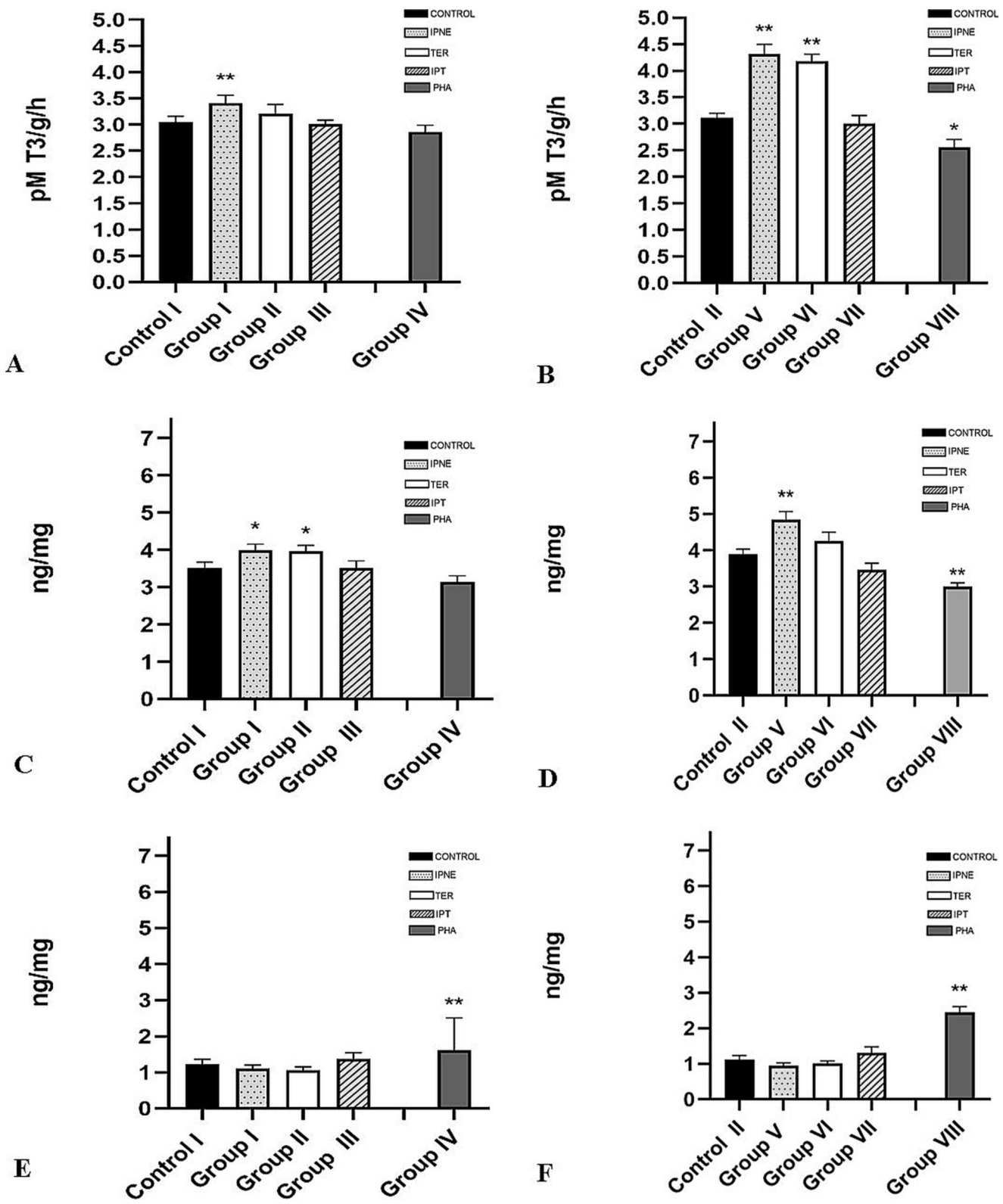

Fig. 2. Hepatic 5'ORD-monodeiodinase (type II) activity (A) and hepatic T_3(C), T_4 (E) content in *Podarcis siculus* subjected to a single intraperitoneally injection of IPNE (Group I), Terb (Group II), IPT (Group III) and PHA (Group IV) and sacrificed 2 h after the last injection. Hepatic 5'ORD-monodeiodinase (type II) activity (B) and hepatic T_3(D), T_4 (F) content in *Podarcis siculus* subjected to 3 intraperitoneally injections of IPNE (Group V), Terb (Group VI), IPT (Group VII) and PHA (Group VIII) and sacrificed 2 h after the last injection. ($p < 0.05$, *$p < 0.01$, **$p < 0.001$, in the comparison with the different controls). A more detailed description is in the text (see Materials and methods section).

Conversely, hepatic T_4 levels increased relative to controls in both experimental conditions. Specifically, a single injection of PHA (Group IV) led to a significant rise in hepatic T_4 compared with controls (1.60 ± 0.89 *vs* 1.23 ± 0.13 ng/mg) (Fig. 2E), while three consecutive injections (Group VIII) produced an even more pronounced increase (2.45 ± 0.15 *vs* 1.12 ± 0.11 ng/mg)(Fig. 2F).

Overall, the results indicate that adrenergic signaling plays a key role in regulating hepatic thyroid hormone metabolism and peripheral thyroid hormone availability. β-adrenergic stimulation is associated with increased 5′-T_4 ORD (type II monodeiodinase) activity, reduced hepatic T_4 content, and a general shift toward enhanced local T_3 production, consistent with an overall activation of thyroid hormone metabolism in the liver. This effect is dose-dependent, being more pronounced after repeated administrations, suggesting a cumulative stimulatory action on deiodinase-mediated conversion processes. In contrast, α-adrenergic blockade with phentolamine produces an opposite hormonal pattern, characterized by a reduction in hepatic T_3 levels and an accumulation of T_4, together with a tendency toward decreased monodeiodinase activity. This suggests an inhibitory influence on peripheral T_4-to-T_3 conversion, leading to altered thyroid hormone balance within the liver. Taken together, these findings support the existence of a finely tuned adrenergic control of thyroid hormone metabolism, where β-adrenergic pathways favor activation of thyroid hormone conversion, whereas α-adrenergic signaling appears to contribute to its restraint. The differential and sometimes opposite effects observed further emphasize the complexity of neuroendocrine regulation of thyroid function in lizards.

3.4. *Effects of β-adrenergic agonists and α-adrenergic antagonist on blood glucose levels*

Overall, both β-adrenergic agonists and the α-adrenergic antagonist induced a clear hyperglycaemic response in lizards, observed after both single and repeated administrations. In particular, after a single administrations IPNE (Group I) and Terb (Group II) produced a significant increase in blood glucose levels compared with controls (Group I: 266 ± 25.3 *vs* 79 ± 15.5 mg/dL; Group II: 219 ± 10.7 *vs* 79 ± 15.5 mg/dL) (Fig. 3A). A significant rise in glycaemia was also detected after a single injection of PHA (Group IV) (156.0 ± 43.5 *vs* 79 ± 15.5 mg/dL) (Fig. 3A).

This hyperglycaemic effect became more pronounced following repeated treatments. Indeed, three administrations of IPNE (Group V) and Terb (Group VI) led to markedly elevated blood glucose levels compared with controls (Group V: 370 ± 40.8 *vs* 91 ± 53.5 mg/dL; Group VI: 357 ± 42.8 *vs* 91 ± 53.5 mg/dL) (Fig. 3B). Similarly, three injections of PHA (Group VIII) also resulted in increased glycaemia relative to controls (274 ± 27.8 *vs* 91 ± 53.5 mg/dL) (Fig. 3B).

The treatment with IPT, both as a single administration and as three injections, does not cause any changes in the blood glucose level (Fig. 3A, B).

Taken together, these findings indicate that both stimulation of β-adrenergic receptors and blockade of α-adrenergic receptors converge on a common metabolic outcome, promoting increased circulating glucose levels. The stronger responses observed after repeated administrations further suggest a cumulative effect of adrenergic modulation on glucose homeostasis, likely reflecting enhanced mobilization of energy reserves and activation of glucose-releasing pathways.

3.5. *Histological analysis after β-adrenergic agonist and α-adrenergic antagonist treatments*

In control thyroid tissue, follicles show a low-columnar follicular epithelium, markedly depleted follicles with retracted colloid, and pyknotic nuclei, indicating a low functional state (Fig. 4 A, B). Treatment with β-adrenergic agonists, both as single and repeated injections, induces a clear increase in follicular epithelial height compared to controls, reflecting enhanced thyroid activity; specifically, single injections of IPNE and Terb produce significant increases (IPNE: 7.15 ± 0.33 μm and Terb: 8.27 ± 0.17 μm *vs* 4.02 ± 0.04 μm) (Table 1), while three injections result in a more pronounced effect, particularly with IPNE (16.20 ± 0.83 μm) (Table 1) and Terb (12.7 ± 0.15 μm) (Table 1), accompanied by numerous colloid reabsorption vacuoles indicative of active hormone release (Fig. 4 C, D). Lizards treated with three injections of IPT (Group VII) exhibited thyroid follicles characterized by a low follicular epithelial height (Table 1), indicative of reduced functional and synthetic activity of the gland. The follicular lumen was filled with compact colloid that lacked resorption vacuoles, suggesting an absence of active colloid reabsorption and consequently a marked reduction in thyroid secretory activity (Fig. 1E). Conversely, histological examination of the thyroid gland following administration of PHA revealed a follicular epithelial height comparable to that observed in the control thyroids (Table 1), a morphological feature generally associated with reduced synthetic activity of the follicular cells. However, despite the low epithelial profile, the colloid displayed numerous resorption vacuoles, indicating active colloid uptake and ongoing hormone release, and therefore suggesting the persistence of secretory activity within the gland (Fig. 4F).

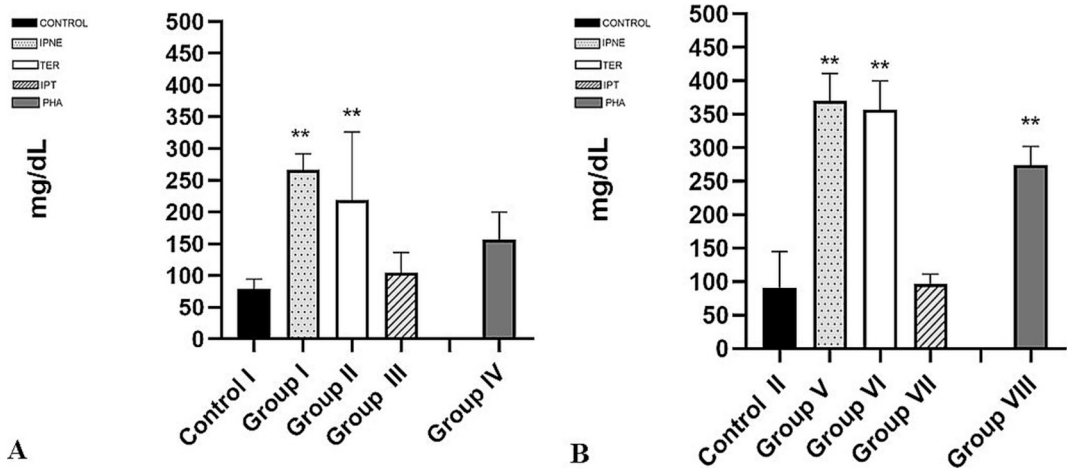

Fig. 3. (A) Plasma glucose levels in *Podarcis siculus* subjected to a single intraperitoneally injection of IPNE (Group I), Terb (Group II), IPT (Group III), or PHA (Group IV) and sacrificed 2 h after the last injection. (B) Plasma glucose levels in *Podarcis siculus* subjected to three intraperitoneally injections of IPNE (Group V), Terb (Group VI), IPT (Group VII), or PHA (Group VIII) and sacrificed 2 h after the last injection. *($p < 0.05$, *$p < 0.01$, **$p < 0.001$,* in compared with the respective controls). A more detailed description is in the text (see Materials and methods section).

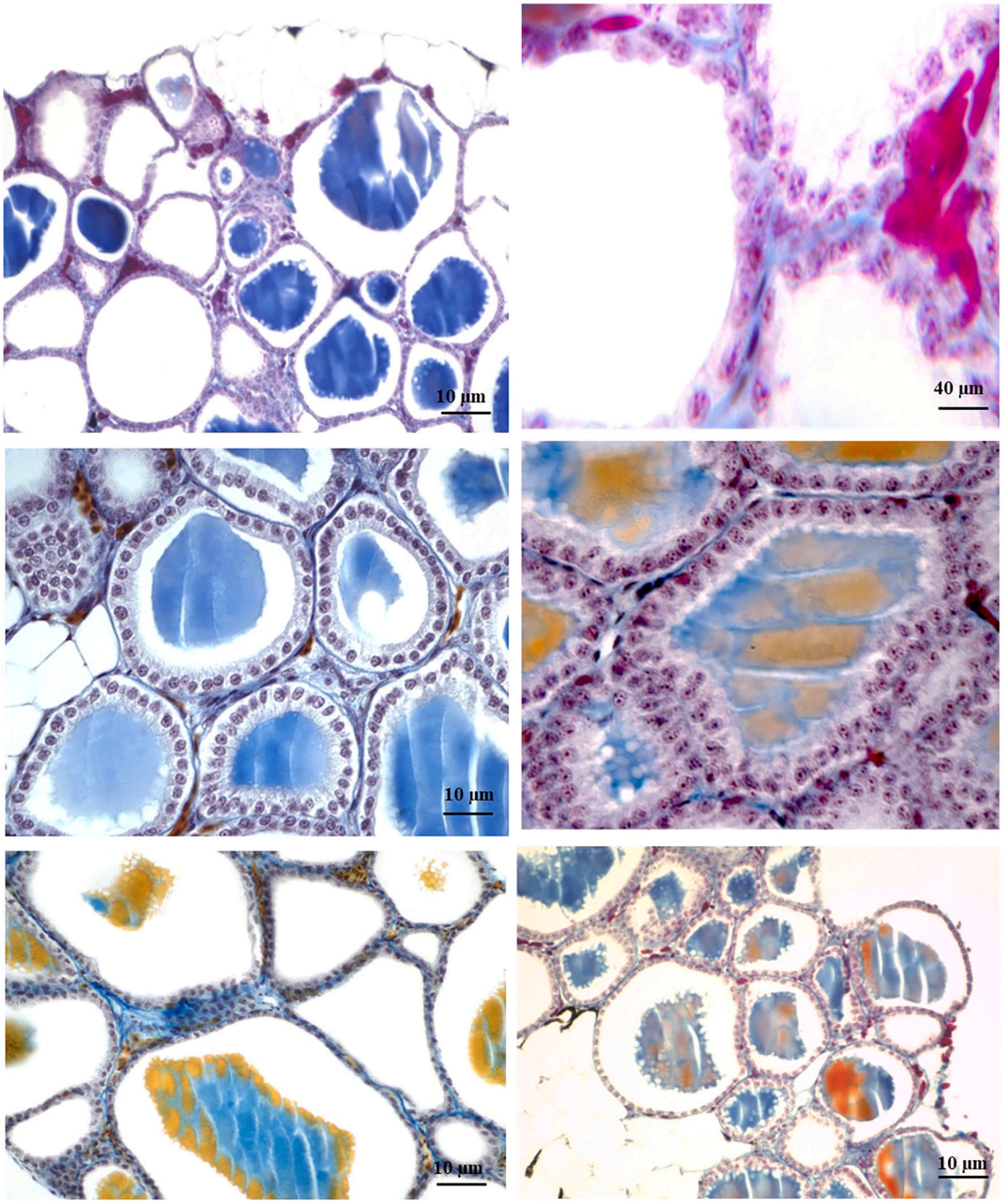

Fig. 4. Thyroid gland of *Podarcis siculus* stained with Galgano I. Scale bars: 10 μm and 40 μm. (A, B) Control lizards captured in November: thyroid follicles exhibit low epithelial height; follicles appear empty, with cells showing pyknotic nuclei, and the colloid is retracted. (C) Lizards treated with three injections of IPNE (Group V): follicular epithelial height is increased, with cuboidal epithelial cells; the colloid contains numerous resorption vacuoles. (D) Lizards treated with three injections of Terb (Group VI): follicular epithelial height is increased, with columnar follicular cells whose nuclei are positioned at approximately three-quarters of the epithelial height; the colloid fully fills the follicular lumen and contains numerous resorption vacuoles. (E) Lizards treated with three injections of IPT (Group VII): follicular epithelial height is low, and the colloid lacks resorption vacuoles. (F) Lizards treated with three injections of PHA (Group VIII): follicular epithelial height is low; follicles contain colloid with numerous resorption vacuoles. A more detailed description is in the text (see Materials and methods section).

Morphometric analysis revealed significant and dose-dependent changes in follicular diameter across the experimental groups, showing a clear inverse correlation with follicular epithelial height. Following a single intraperitoneal injection, a marked reduction in follicular diameter was observed in both the IPNE (Group I: 225 ± 15 μm) and Terb (Group II: 184 ± 10 μm) groups compared to the physiological solution control (345 ± 20 μm; $p < 0.001$) (Table 2). This shrinkage was further exacerbated after three consecutive injections, where the IPNE-treated animals (Group V) exhibited the most dramatic drop in follicular size, falling to 101 ± 10 μm—a nearly 3.5-fold reduction relative to controls (Table 2). Similarly, the triple-injection Terb group (Group VI) maintained a significantly reduced diameter of 123 ± 10 μm ($p < 0.001$) (Table 2). In contrast, IPT administration caused only a mild, non-significant decrease in follicular diameter after a single dose (Group III: 287 ± 10 μm) and after three doses (Group VII: 297 ± 15 μm) (Table 2). Finally, PHA treatment led to minor reductions

Table 1
Epithelial height (μm) in the thyroid gland of *Podarcis siculus* after treatment. Animals received either a single intraperitoneally injection of IPNE (Group I), Terb (Group II), IPT (Group III), and PHA (Group IV), and three intraperitoneally injections of IPNE (Group V), Terb (Group VI), IPT (Group VII), and PHA (Group VIII) and were sacrificed 2 h after the last injection. Data are expressed as epithelial height, with significant differences compared to the respective controls indicated as $p < 0.05$, *$p < 0.01$, **$p < 0.001$. For detailed methodology, see the Materials and methods section.

Substances	Epithelial height (μm)			
	A single intraperitoneally injection and sacrificed after 2 h after injection		Three intraperitoneally injections and sacrificed after 2 h after injection	
Physiological solution	Control Group	4.02 ± 0.04	Control Group	4.02 ± 0.04
IPNE	Group I	7.15 ± 0.33 **	Group V	16.2 ± 0.83 **
Terb	Group II	8.27 ± 0.17 **	Group VI	12.7 ± 0.15 **
IPT	Group III	4.15 ± 0.11	Group VII	5.28 ± 0.12*
PHA	Group IV	3.16 ± 0.08*	Group VIII	4.08 ± 0.05

Table 2
Follicular diameter (μm) in the thyroid gland of *Podarcis siculus* after treatment. Animals received either a single intraperitoneally injection of IPNE (Group I), Terb (Group II), IPT (Group III), and PHA (Group IV), and three intraperitoneally injections of IPNE (Group V), Terb (Group VI), IPT (Group VII), and PHA (Group VIII) and were sacrificed 2 h after the last injection. Data are expressed as epithelial height, with significant differences compared to the respective controls indicated as $p < 0.05$, *$p < 0.01$, **$p < 0.001$. For detailed methodology, see the Materials and methods section.

Substances	Follicular diameter (μm)			
	A single intraperitoneally injection and sacrificed after 2 h after injection		Three intraperitoneally injections and sacrificed after 2 h after injection	
Physiological solution	Control Group	345 ± 20	Control Group	345 ± 20
IPNE	Group I	225 ± 15**	Group V	101 ± 10**
Terb	Group II	184 ± 10**	Group VI	123 ± 10**
IPT	Group III	287 ± 10*	Group VII	297 ± 15*
PHA	Group IV	305 ± 20	Group VIII	325 ± 25

in follicular size (Group IV: 305 ± 20 μm; Group VIII: 325 ± 25 μm), which remained close to control values, consistently with the low epithelial activation observed in these groups (Table 2). Together, these data demonstrate that the rapid increase in cell height induces a concurrent, profound contraction of the overall follicular structure due to massive colloid depletion.

The semi-quantitative scoring of colloid resorption vacuoles strictly confirmed the morphometric findings of follicular epithelial height and follicular diameter (Table 3). In both the single-injection and triple-injection protocols, control groups and IPT-treated animals exhibited absent or rare vacuoles (Scores <0.20) (Table 3). Conversely, a single injection of IPNE (Group I) and Terb (Group II) induced a significant appearance of resorption vacuoles, reaching moderate-to-high scores (1.85 ± 0.15 and 2.20 ± 0.10, respectively; $p < 0.001$ *vs.* Control) (Table 3). This effect was even more pronounced after three injections, where the IPNE group (Group V), which displayed the maximum epithelial height, consistently reached a near-maximal vacuole score (2.95 ± 0.05; $p < 0.001$), indicating massive colloid endocytosis and extensive erosion of the follicular lumen perimeter. Finally, PHA treatment (Group IV) resulted in a complete absence of resorption vacuoles (Score = 0), perfectly matching the observed reduction in epithelial height (Table 3).

Table 3
Semi-quantitative scoring of colloid resorption vacuoles in thyroid follicles. Data are expressed as mean values ± standard error (SE), followed by the predominant morphological score (0–3) in parentheses. Animals received both a single intraperitoneally (i.p.) injection and three i.p. injections and were sacrificed 2 h after the final administration. Significant differences compared to the respective controls indicated as $p < 0.05$, *$p < 0.01$, **$p < 0.001$. For detailed methodology, see the Materials and methods section.

Substances	Resorption vacuole (Score 0–3)			
	A single intraperitoneally injection and sacrificed after 2 h after injection		*Three intraperitoneally injections and sacrificed after 2 h after injection*	
Physiological solution	Control Group	0.10 ± 0.04 (Score **0**)	Control Group	0.10 ± 0.04 (Score 0)
IPNE	Group I	1.85 ± 0.15 (Score **2**)**	Group V	2.95 ± 0.05 (Score **3**)**
Terb	Group II	2.20 ± 0.10 (Score **2**)**	Group VI	2.60 ± 0.12 (Score **3**)**
IPT	Group III	0.15 ± 0.05 (Score **0**)	Group VII	0.65 ± 0.11 (Score **1**)*
PHA	Group IV	0.00 ± 0.00 (Score **0**)	Group VIII	0.12 ± 0.04 (Score **0**)

4. Discussions

The present study demonstrates that adrenergic signaling exerts a profound regulatory influence on thyroid activity, peripheral thyroid hormone metabolism, and energetic homeostasis in *Podarcis siculus*. The combined biochemical and histological results indicate that β-adrenergic stimulation promotes activation of the thyroid axis and peripheral thyroid hormone conversion, whereas α-adrenergic blockade produces an overall inhibitory effect on thyroid hormone metabolism despite stimulating pituitary TSH secretion. These results support the existence of a complex adrenergic control of the hypothalamic–pituitary–thyroid axis in reptiles (Sciarrillo et al., 2025; Rasmussen et al., 2021).

The reduction in circulating TSH levels observed after administration of the β-adrenergic agonists IPNE and Terb appears paradoxical when considered together with the marked increase in plasma T_3 and T_4 concentrations. However, this pattern is consistent with a negative feedback mechanism exerted by elevated thyroid hormones on pituitary thyrotropic cells. The strong increase in circulating T_3 and T_4, particularly after repeated administrations, suggests that β-adrenergic stimulation directly enhances thyroid secretory activity independently of pituitary stimulation.

A particularly intriguing finding in our study involves the dual endocrine paradoxes observed within the hypothalamic-pituitary-thyroid (HPT) axis framework under different treatments. First, β-agonist administration triggered a significant decrease in circulating TSH alongside a concomitant rise in T_3 and T_4 levels. While systemic negative feedback loops are highly plausible, the short 2-h experimental window suggests that classical central pituitary-hypothalamic feedback kinetics, which are typically prolonged in ectotherms, may not fully account for this rapid divergence. Instead, this phenomenon strongly points toward a direct, non-classical adrenergic action on thyroid follicular cells bypassing central TSH control. Mechanistic studies in comparative endocrinology demonstrate that thyroid follicular cells express functional β-adrenergic receptors. Activation of these receptors by agonists like IPNE or Terb directly stimulates adenylate cyclase, inducing a rapid intracellular cAMP-mediated cascade that triggers follicular lumen endocytosis and immediate thyroid hormone release. This autonomous peripheral surge of T_3 and T_4 would subsequently execute a rapid, short-loop suppression of pituitary TSH (Calebiro et al., 2009).

The concurrent evaluation of follicular epithelial height, follicular diameter, and resorption vacuolar score provides a comprehensive

morphofunctional overview of thyroid gland dynamics under the tested substances. In our study, a clear biological synchrony was observed among these three parameters, particularly under IPNE and Terb stimulation. The dramatic increase in epithelial height, reaching its peak in the multi-injection IPNE group (16.2 ± 0.83 μm), was strictly coupled with a near-maximal resorption vacuole score (2.95 ± 0.05) and a prominent, 3.5-fold reduction in overall follicular diameter (101 ± 10 μm). Biologically, this triad of morphological alterations represents the classic hallmark of intense thyroid hyperactivity. The rapid, stimulus-induced elongation of thyrocytes reflects an accelerated synthetic and secretory state, while the extensive formation of apical resorption vacuoles directly visualizes the massive endocytosis of intraluminal colloid. Consequently, this rapid depletion of colloid stores deprives the follicle of its internal volume, leading to a profound physical contraction of the follicular structure, as evidenced by the significantly shrunken diameters. Taken together, these highly correlated morphometric data demonstrate that IPNE and Terb act as potent triggers of immediate thyroid activation, profoundly remodeling both the cellular architecture and the macroscopic follicular compartments.

The stimulatory effects of β-adrenergic agonists on thyroid hormone secretion were paralleled by marked alterations in hepatic thyroid hormone metabolism (Mebis and Van den Berghe, 2009). Increased activity of hepatic 5′-T_4 ORD (type II monodeiodinase), together with elevated hepatic T_3 and reduced T4 content, indicates enhanced peripheral conversion of T_4 into the biologically active hormone T_3. (Sciarrillo et al., 2025; Thambirajah et al., 2022). These findings suggest that β-adrenergic pathways not only stimulate thyroidal hormone release but also amplify peripheral thyroid hormone activation at the tissue level. Such coordinated regulation may represent an adaptive metabolic response aimed at increasing energetic turnover and supporting elevated metabolic demands. Reptiles, whose physiology is strongly dependent on environmental and seasonal conditions, may particularly benefit from neuroendocrine mechanisms capable of rapidly modulating metabolic activity in response to external stimuli (Bianco et al., 2018; Holzer and Laudet, 2015).

In contrast, treatment with the α-adrenergic antagonist PHA produced a markedly different endocrine profile. Plasma TSH levels increased significantly after both single and repeated administrations, indicating that α-adrenergic pathways may normally exert a stimulatory influence on thyroid hormone secretion or participate in inhibitory feedback regulation at the pituitary level. Despite elevated TSH concentrations, circulating and hepatic T_3 levels decreased, while hepatic T_4 accumulated, suggesting impaired thyroid hormone synthesis and reduced peripheral T_4-to-T_3 conversion. The reduction in deiodinase activity observed after PHA treatment further supports this interpretation. Therefore, blockade of α-adrenergic receptors appears to disrupt normal thyroid hormone activation and utilization. Interestingly, histologically, the absence of vacuolization, combined with epithelial flattening and unchanged follicular size in the PHA and IPT groups, confirms the lack of follicular recruitment.

This inverse endocrine pattern triggered by PHA, characterized by elevated circulating TSH accompanied by significantly decreased T_3 concentrations, suggests a state of functional TSH-refractoriness at the follicular level. Adrenergic signaling pathways are known to cross-talk with and modulate follicular sensitivity to TSH. The administration of the antagonist PHA likely disrupts the basal adrenergic tone required for normal thyroid responsiveness, uncoupling the TSH receptor from its downstream G-protein or cAMP signaling networks. Consequently, the thyroid gland becomes temporarily refractory to circulating TSH, failing to synthesize or secrete T_3. In response to this acute peripheral thyroid resistance and the dropping levels of active thyroid hormones, the pituitary gland initiates a compensatory upregulation of TSH secretion, culminating in the observed paradox. These findings highlight that adrenergic regulation of reptile metabolism is a complex multi-layered system, acting not only through central endocrine orchestration but also *via* direct, localized receptor dynamics within the peripheral glandular epithelium.

A compelling finding in our study was that 1-isopropylamino-3-(2-thiazoloxy)-2-propanol (ITP) consistently exerted no significant effects, failing to replicate the robust responses triggered by the non-selective β-agonist isoproterenol (IPNE) and the selective β_2-agonist terbutaline (Terb). In comparative pharmacology, ITP is classified as a highly selective β_1-adrenergic partial agonist; it acts as a stimulant on cardiac tissue but typically lacks intrinsic activity or acts as a functional antagonist on smooth muscle and metabolic pathways regulated by β_2 or β_3) receptors. Because definitive adrenoceptor-subtype expression data and specific selectivity profiles for ITP remain entirely uncharacterized in reptiles, this distinct negative result provides an important functional clue. The failure of the β_1-selective ITP to trigger a physiological response, contrasted with the marked effects of IPNE and Terb, strongly suggests that β_2- or potentially β_3-adrenergic pathways, rather than a β_1-dependent mechanism primarily drive the downstream ecophysiological cascades evaluated here (such as MDA accumulation).

Another important aspect emerging from the present study concerns glucose metabolism. Both β-adrenergic stimulation and α-adrenergic blockade induced marked hyperglycaemia, particularly after repeated administrations. Catecholaminergic pathways are known to regulate glycogenolysis and gluconeogenesis in vertebrates, and the observed increase in circulating glucose likely reflects mobilization of energetic substrates to sustain enhanced metabolic activity (Mullur et al., 2014). In β-agonist-treated animals, the simultaneous increase in thyroid hormone levels may further contribute to elevated glucose availability by stimulating overall metabolic rate. The hyperglycaemic effect observed after PHA administration suggests that α-adrenergic mechanisms also participate in glucose homeostasis, possibly through modulation of hepatic carbohydrate metabolism or pancreatic endocrine function.

Taken together, the present findings demonstrate that adrenergic pathways play a central role in coordinating endocrine and metabolic responses in *Podarcis siculus*. β-adrenergic signaling promotes thyroid activation, peripheral thyroid hormone conversion, and metabolic mobilization, whereas α-adrenergic blockade interferes with these processes and alters the balance of thyroid hormone metabolism. The differential responses observed at pituitary, thyroidal, hepatic, and histological levels emphasize the complexity of neuroendocrine regulation in reptiles and suggest that adrenergic mechanisms contribute significantly to the adaptive control of energy metabolism and thyroid function. Further studies investigating receptor localization, intracellular signaling pathways, and seasonal influences could help clarify the mechanisms underlying adrenergic regulation of the reptilian thyroid axis.

5. Conclusion

Overall, these findings highlight the importance of adrenergic mechanisms in the neuroendocrine control of the hypothalamic–pituitary–thyroid axis in reptiles and show that adrenergic pathways in *Podarcis siculus* tightly regulate thyroid activity and peripheral hormone metabolism. In ectotherms, where physiological performance is strongly influenced by environmental variables such as temperature and season, adrenergic signaling likely functions as an integrative system that links external stimuli to endocrine and metabolic responses. β-adrenergic activation enhances thyroid hormone secretion and peripheral T_4-to-T_3 conversion, supporting increased metabolic activity and energy mobilization when physiological demands rise. In contrast, α-adrenergic pathways appear to contribute to limiting thyroid activation and maintaining metabolic balance. The coordinated effects observed on thyroid hormones and glucose levels further suggest that adrenergic regulation synchronizes endocrine output with energy availability, ensuring an appropriate metabolic response to changing conditions. Overall, adrenergic control of the thyroid axis may represent an adaptive mechanism that allows reptiles to rapidly adjust metabolic activity to environmental fluctuations, supporting survival in variable

ecological contexts.

CRediT authorship contribution statement

Francesca Carrella: Writing – original draft, Conceptualization. **Assunta Lallo:** Software, Methodology, Data curation. **Vito Gallicchio:** Visualization, Validation. **Stefania Boccia:** Software, Data curation. **Benedetta Sangarella Valvano:** Software, Data curation. **Maria De Falco:** Validation, Software. **Rosaria Sciarrillo:** Writing – review & editing, Supervision.

Author's statement

All authors have contributed to the manuscript that they approve for publication. The manuscript has no conflict of interest. In agreement with my co-authors, I declare that the submitted work is original research that has not been previously published and is not under consideration for publication elsewhere, in whole or in part.

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The authors have no competing financial interests or personal relationships that could influence the work reported in this article.

Appendix A. Supplementary data

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Data availability

Data will be made available on request.

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