FROM TISSUE ARCHITECTURE TO HORMONAL REGULATION: AN INTEGRATIVE MULTIMODAL STUDY OF ENDOCRINE ORGAN ADAPTATION TO CHRONIC MYCOBACTERIAL INFLAMMATION IN RATS

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Relevance. Chronic infection and the sustained inflammation that accompanies it affect several endocrine organs at the same time, yet most experimental studies examine a single gland or a single analytical level. As a result, the way in which the endocrine system as a whole re-organises itself under prolonged immune stress - and how this depends on age - remains insufficiently characterised. An integrated approach that follows the response from tissue architecture through cellular and molecular markers to hormonal output offers a more complete understanding of endocrine adaptation.

A controlled model of chronic granulomatous inflammation, induced by mycobacteria, provides a reproducible platform for such an analysis and links morphological findings to their functional consequences, which is important for interpreting endocrine involvement in chronic infectious and inflammatory diseases.

Aim. To provide an integrative, multimodal characterisation of the age-dependent response of the thyroid and adrenal glands to chronic mycobacterial inflammation, spanning morphometric, histochemical, immunohistochemical and hormonal levels of analysis.

Materials and methods. Outbred white male rats aged 4 and 9 months were studied (four groups; n=20 per group). Experimental animals received a single subcutaneous injection of Freund's adjuvant containing killed Mycobacterium tuberculosis; intact animals served as controls, with a one-month observation period. The thyroid and adrenal glands were examined by haematoxylin–eosin morphometry, van Gieson and Alcian blue histochemistry, and immunohistochemistry (Caspase-3, CD68, p53, inhibin) quantified with QuPath-0.5.1 (×200). Serum hormones were measured and compared using an artificial-intelligence (AI)-assisted analysis. Data are given as M±m; $p<0.05$.

Results. Across all analytical levels, mycobacterial exposure produced a coordinated but organ-specific response that intensified with age (Table 1). In the thyroid, follicular atrophy with colloid resorption, macrophage infiltration and increased interstitial collagen was accompanied by a sharp rise in Caspase-3 and CD68 expression and by a decrease in thyroid hormones (T3, T4, free T4), indicating apoptotic-inflammatory injury with a tendency to hypofunction. In the adrenal cortex, thinning of the zona fasciculata with corticocyte lipid depletion, sinusoidal dilation, immune-cell infiltration and marked accumulation of glycosaminoglycans was accompanied by reduced p53 and inhibin expression and by increased cortisol, ACTH and aldosterone, indicating steroidogenic activation of the hypothalamic–pituitary–adrenal axis. The AI-assisted analysis separated the thyroid ("regulatory decline") and adrenal ("activation") profiles as distinct clusters.

Table 1.

Integrated direction of change (mycobacteria vs control) across analytical levels

Analytical level	Thyroid gland	Adrenal gland
Parenchymal morphometry	Follicle diameter ↓, thyrocyte height ↓	Zona fasciculata thickness ↓
Secretory / functional cell state	Colloid resorption ↑	Corticocyte lipid ↓ (steroidogenesis ↑)
Microvasculature	Vessel diameter ↑, perifollicular flow ↑	Sinusoid diameter ↑, hyperaemia
Macrophages (CD68)	↑↑	↑
Apoptosis / cell-stress	Caspase-3 ↑↑	p53 ↓
Cell differentiation	—	Inhibin ↓
Stromal remodelling	Collagen/fibrosis ↑ (van Gieson)	Glycosaminoglycans ↑↑ (Alcian blue)
Hormonal output	T3, T4, free T4 ↓ (hypofunction)	Cortisol, ACTH, aldosterone ↑ (HPA activation)

Discussion. The two glands responded in a coordinated yet divergent manner: the thyroid underwent predominantly destructive, apoptotic-inflammatory injury leading to functional decline, whereas the adrenal showed steroidogenic activation progressing towards decompensation (vacuolisation, fatty dystrophy) with age. This organ-specific divergence reflects the integrated neuroendocrine–immune response to chronic mycobacterial inflammation, in which cytokine-driven activation of the HPA axis coexists with suppression of peripheral thyroid activity. The concordance of structural, histochemical, immunohistochemical and hormonal changes at both ages validates the model and demonstrates the value of a multimodal, AI-supported strategy for detecting patterns that are not apparent from any single method. The consistently greater response at 9 months indicates an age-related decline in endocrine adaptive reserve.

Conclusion. Chronic mycobacterial inflammation produces a coordinated, age-dependent, multi-level remodelling of the endocrine glands that integrates structural, cellular, molecular and hormonal changes into a single adaptive response — the thyroid trending towards hypofunction and the adrenal towards activation and eventual decompensation. The integrative, multimodal design provides a comprehensive framework for studying endocrine involvement in chronic inflammatory and infectious conditions.

Keywords: *endocrine glands, thyroid, adrenal, mycobacteria, morphometry, histochemistry, immunohistochemistry, hormonal profiling, artificial intelligence, age-dependent adaptation.*

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