Antithyroid Substances and Naturally Occurring Goitrogens

Antithyroid Substances and
Naturally Occurring Goitrogens

Pavel Langer

Head of the Thyroid Laboratory, Institute of Experimental Endocrinology
Slovak Academy of Sciences, Bratislava, Czechoslovakia

Monte A. Greer

Head of the Division of Endocrinology, Department of Medicine
University of Oregon Health Science Center, Portland, Oreg., USA

44 figures and 17 tables, 1977

S. Karger • Basel • München • Paris • London • New York • Sydney

Cataloging in Publication
Langer, Pavel
1. Thyroid Antagonists 2. Goiter - etiology I. Greer, Monte A. II. Title
WK 202 L276a
ISBN 3-8055-2659-8

All rights, including that of translation into other languages, reserved. Photomechanic reproduction (photocopy, microcopy) of this book or part of it without special permission of the publishers is prohibited.

© Copyright 1977 by S. Karger AG, Basel (Switzerland), Arnold-Böcklin-Strasse 25
ISBN 3-8055-2659-8

Contents

1. Brief Historical Introduction 1
2. Chemical Classification of Antithyroid Substances 3
   I. Inorganic compounds with antithyroid effect 3
      A. Complex univalent anions 3
      B. Miscellaneous anions and cations 3
   1. Calcium 3
2. Molybdate 4
3. Cobalt 4
4. Lithium 4
5. Iodide 5

II. Organic compounds with antithyroid effect 5
A. Thionamides 5
1. Thioureas 6
2. Thiouracils 6
3. Mercaptoimidazoles 6
4. Miscellaneous thionamides 7
   a. Thiobarbiturates 7
   b. Goitrin (L-5-vinyl-2-thiooxazolidone) 7
B. Aniline derivatives and aminoheterocyclic compounds 7
C. Substituted phenols 9
D. Miscellaneous organic compounds 10
1. Butyl-3,5-diido-4-hydroxybenzoate (BDHB) 10
2. Antibiotics 10
3. 1,1,3-tricyano-2-amino-1-propene 10
4. Reserpine 10
5. Phenylbutazone (Butazolidine) 10
6. Phenazone 11
7. 2,3-dimercapto-propanol (BAL - British Anti-Lewisite) 11
8. Purine derivatives 11
9. Membrane-active agents 11
10. Naturally occurring goitrogens 11
11. Tyrosine analogues 11

3. Metabolism of Antithyroid Substances 12
I. Absorption, blood levels and urinary excretion of antithyroid drugs and
   the duration of their inhibitory action 12
II. Extrathyroidal metabolism of antithyroid drugs 15
III. Intrathyroidal metabolism of antithyroid drugs 16

4. Intrathyroidal Effects of Antithyroid Compounds 20
I. Inhibition of the iodide pump 22
   A. Mechanism of action 24
   II. Inhibition of iodination of thyroglobulin 24
      A. Iodide potentiation of action 29

Contents VI

B. Differences in sensitivity to inhibition of thyroid biosyntheses by antithyroid
drugs in thyroids in intact and hypophysectomized rats 29
C. Mechanism of action 30
5. Effects of Antithyroid Substances and Other Factors on Extrathyroidal Metabolism of Iodide and Thyroid Hormone

I. Iodine compounds in blood and kinetics of their transfer to the tissues

A. Estimation of iodine compounds in blood
   1. Protein-bound iodine (PBI) and butanol-extractable iodine (BEI)
   2. Total thyroxine and triiodothyronine concentration in serum
   3. Inorganic iodide in plasma

B. Binding of thyroid hormones to plasma proteins

C. Free or unbound fraction of thyroid hormones in plasma
   1. Equilibrium dialysis or ultrafiltration for estimation of free T4 and T3
   2. T3 uptake tests
   3. Free thyroxine index

D. Turnover of thyroid hormones

E. Distribution of thyroid hormones and their transfer to tissue

II. Effects on metabolism, distribution and balance of iodide

III. Various extrathyroidal effects on blood thyroid hormone concentration and metabolism

A. Chemical, pharmacological and physiological effects (drugs, endogenous and exogenous hormones, muscular exercise)
   1. Salicylate and dinitrophenol (DNP)
   2. Diphenylhydantoin (DPH)
   3. Heparin
   4. Steroid hormones and analogues
      a) Androgenic-anabolic steroids and glucocorticoids
      b) Estrogens and pregnancy
      c) Adrenal steroids
   5. Thionamides and other organic thiocompounds
   6. Thiocyanate and other univalent anions
   7. Miscellaneous chemical and pharmacological effects
      a) Effect of various compounds in vitro
      b) Diazod dyes and some other compounds
      c) Thyrotropic hormone
      d) Reserpine
      e) Ether and barbiturates
      f) Sulphonylureas
      g) Antibiotics
      h) Hypolipidemic agents
      i) Anti-inflammatory drugs
      j) Narcotics
   8. Chemical effects on fecal reabsorption of thyroxine
   9. Muscular exercise
B. Pathological effects 65
1. Acute infection 65
2. Liver disease 66
3. Miscellaneous diseases 67
4. Surgery 67

Contents VII

5. High altitude 68
6. Genetic disorders 68

6. The Influence of Antithyroid Substances on Hypothalamo-pituitary-thyroid Integration 69
I. Various mechanisms by which plasma thyroid hormone concentration can be decreased and the resultant effect on pituitary-thyroid interplay 70
II. Changes of pituitary TSH secretion due to the action of antithyroid compounds and thyroidectomy 72
A. Acute changes of radioiodine release from thyroid 72
B. Acute changes of radioiodine uptake 74
C. Changes in blood and pituitary TSH concentration after the administration of antithyroid compounds 76
D. Changes in blood and pituitary TSH concentration after thyroidectomy 76
III. General aspects of a steady state of hypothalamo-pituitary-thyroid function and its long-term changes 77

7. Naturally Occurring Goitrogens 79
I. Chemical nature of goitrogens in plants and food 79
A. Cyanates 79
B. Onion volatiles 80
C. Soy beans, groundnuts, etc 80
D. Thiocyanate 81
E. Thiooxazolidones 82
F. Isothiocyanates (mustard oils) 85
II. Techniques for estimation of glucosinolates and their aglucones 86
A. Inactivation of naturally occurring myrosinase 87
1. Seeds 87
2. Green parts 88
B. Preparation of myrosinase (thioglucosidase or thioglucoside glucohydrolase - EC 3.2.3.1) 88
C. Identification of glucosinolates 88
D. Optimum conditions for the formation of aglucones by the action of myrosinase 89
1. Time 90
2. Temperature 91
3. pH 91
4. Other conditions 91
E. Estimation of liberated aglucones 92
1. Steam distillation 92
2. Extraction of liberated isothiocyanates and thiooxazolidones from the reaction mixture with organic solvents 92
3. Conversion of the extracted isothiocyanates into corresponding thioureas and their chromatographic separation 93
4. UV-absorption spectrophotometry 94
F. Qualitative and quantitative composition of aglucones in cabbage 95
1. Thiocyanate 95
2. L-5-vinyl-2-thiooxazolidone 95
3. Isothiocyanates 95
III. Identity of “Brassica-factor” 96
A. Inhibition of thyroid function following a single feeding of vegetables in guinea pigs 98

Contents VIII

B. Goitrogenic effect of cabbage in guinea pigs and rats in long-term experiments with a controlled iodine intake 99
C. Estimation of the individual compounds in cabbage and their daily intake in rats 100
1. Thiocyanate 100
2. Isothiocyanates and thiooxazolidones 101
a) Inactivation of myrosinase and extraction of plant material 101
b) Enzymatic splitting and ether extraction 101
c) Quantitative estimation of the total ether-volatile and ether nonvolatile aglucones with the aid of UV-spectrophotometry 101
A. Iso thiocyanate 101
B. Thiooxazolidones 103
3. Daily intake of goitrogenic aglucones 103
D. Examination of the antithyroid effect of the individual aglucones in relation to their concentration in cabbage 103
1. Thiocyanate 103
2. Isothiocyanates 108
3. Thiooxazolidones 110
E. Simulation of the goitrogenic effect of cabbage by simultaneous administration of thiocyanate, isothiocyanate, and thiooxazolidone 111
F. The additive antithyroid effect of thiocyanate, isothiocyanate, and thiooxazolidone 113
IV. Metabolism of the most important natural goitrogens 116
A. Biosynthesis of glucosinolates in plants 116
B. Decomposition of glucosinolates during the processing of foods and digestion in the gastrointestinal tract 120
C. Metabolism of the individual aglucones in man and mammals 121
1. Thiocyanate 121
   a) Endogenous formation of thiocyanate 121
   b) Exogenous preformed thiocyanate 123
   c) Distribution of thiocyanate in the organism 124
   d) Metabolic conversion of thiocyanate 124
   e) Thiocyanate balance in experimental animals and in man 125
2. Isothiocyanates 126
3. Thiooxazolidones 128
V. The role of goitrogens in the etiology of endemic and sporadic goiter 129
A. Present status of natural goitrogenes in animal and human nutrition 130
B. Natural goitrogens and the human thyroid 133
C. Interrelation between goitrogenic and thiocyanogenic properties of food 135
D. The effect of foods and pure goitrogenic aglucones on human thyroid 138
1. Thiocyanate 139
2. Goitrin (L-5-vinyl-2-thiooxazolidone) 140

2. The Clinical Use of Antithyroid Drugs 141
I. Choice of patients 141
II. Plan of therapy 142
III. Management 143
IV. Complications 144
A. Drug toxicity 144
1. Rash 144

Contents IX

2. Agranulocytosis 144
3. Jaundice 145
B. Hypothyroidism 145
C. Progressive thyroid enlargement 145
D. Progressive ophthalmopathy 146
V. Rapid therapy 147
VI. Ancillary therapy 148
A. frontmatter
   -adrenergic blockers 148
B. Phenobarbital 148
C. Tranquilizers 148
VII. Long-term results 149
Acknowledgement

We are deeply indebted to Susan Jones, without whose expert editorial and secretarial guidance this monograph might never have seen print. The personal investigations described herein were supported by the Slovak Academy of Sciences, Bratislava, Czechoslovakia, and the National Institute of Arthritis, Metabolic and Digestive Diseases, National Institutes of Health, USA.