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HORMONAL THERAPY IN PAEDIATRICS

E S S A Y

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To: My

Parents

My first teachers in life.



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INTRODUCTION

INTRODUCTION

It has been said that "knowledge is of two kinds: we know the subject ourselves, or we know where we can find information on it." The speed of progress of Endocrinology and Metabolism continues to be so rapid that pursuit even of the second approach is difficult, thus justifying the preparation of this essay to discuss some recent trends in hormonal therapy in the paediatric age group.

The endocrine system adjusts and correlates the activities of the various body systems, making them appropriate to the changing demands of the external and internal environment. This integration is brought about by the hormones, which are chemical messengers produced by ductless glands that are transported in the circulation to target cells, where they regulate the metabolic processes.

It is worthy of note that the leadership of the endocrine orchestra has now passed from the pituitary to the hypothalamus.

Hormonal therapy in paediatric practice has such a wide scope, which has extended beyond application in endocrinal disorders, to cover other fields in paediatrics such as Cardiology, Nephrology, Pneumatology and Haematology.

AIM OF THE REVIEW

Our goal in presenting this essay is to collect relatively short, yet fairly comprehensive reviews of hormonal therapy of

endocrinal disorders in pediatric practice, together with the up-to-date uses of hormones in some other paediatric fields.

METHODOLOGY

The subject will be taceled according to the individual glands:

- 1- Hypothalamus.
- 2- Pituitary gland: anterior and posterior.
- 3- Thyroid gland.
- 4- Parathyroid glands.
- 5- Adrenals.
- 6- Gonads.
- 7- Pacreas.

The various diseases of those glands together with their management will be reviewed. In reviewing management, the established old lines of therapy will be discussed fast.

This will be followed by reviewing recent trends in the field.

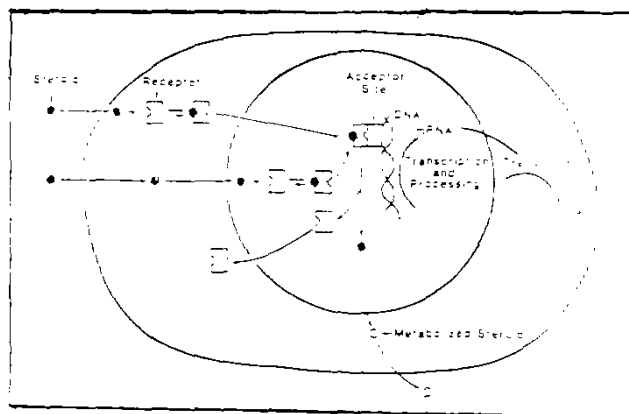
SPOTLIGHTS ON MECHANISM OF HORMONAL ACTION

A hormone is classically defined as a physiological regulator synthesised by ductless glands and transported in plasma to act on target cells at a distant site. How the specificity of action is conferred remained unknown until target tissue was shown to contain receptors to which the hormone bound (Baxter and Funder, 1979).

Hormones can be divided into two classes on the basis of their lipid solubility and mechanisms of action. Those hormones that are lipid soluble (thyroid and steroid hormones) traverse the lipid-rich membranes of the target cell and interact with intracellular components (Fig. A).

The non- protein bound or 'free' fraction of steroid in plasma enters target cells by passive diffusion where a specific, high affinity, low capacity cytoplasmic protein binds the steroid (Evans et al, 1984).

Figure A. MECHANISMS OF STEROID HORMONE ACTION
General Model of Steroid Hormone Action



Evans et al, 1984

Once formed the steroid receptor complex is activated by a presumed structural alteration to the receptor and translocated to the nucleus where it binds to acceptor sites on chromatin. Subsequent events are incompletely understood but there follows DNA directed, RNA mediated new protein synthesis and expression of biological function of the steroid. This unified complex applies to all classes of steroid hormones except androgens. Testosterone; the principal circulating androgen, is converted intracellularly by a 5 α reductase enzyme to an active metabolite, dihydrotestosterone, before receptor binding (Hughes, 1984).

Water-soluble hormones, including the peptide hormones and catecholamines, do not readily traverse the lipid barrier posed by the plasma membrane of the cell but interact directly with receptors located on the cell surface (Fig. B).

As shown in table A, the chemical nature of the individual hormone determines many features of how the hormone operates biochemically, especially its interaction with its target cells (Roth and Grunfeld, 1985).

Table A. COMPARISON OF TWO CLASSES OF HORMONES

		Peptides	Steroids
Solubility*	-in aqueous(polar)solvents -in nonaqueous(nonpolar) solvents	excellent poor	limited excellent
Synthesis and Degradation	-biosynthetic pathway -extraglandular trans- formation of bioactivity -storage of preformed hormone -degradation products	single peptide;pro- hormones very rare often substantial irreversibly inactive	multiple enz- ymes common minimal sometimes retain or re- gain activity
In Plasma	-binding proteins -half-life	very rare short(minutes)	yes long(hours)
At Target Cell	-initial binding site -principal site of action -principal mechanism of action	cell-surface receptor plasma membrane stimulate production of soluble intracell- ular("second")messenger	cytoplasmic re- ceptor nucleus stimulate pro- duction of specific mRNAs

Catecholamines follow patterns of peptide hormones except that biosynthesis is via a multienzyme pathway like that for steroids and $1,25(\text{OH})_2$ vitamin D. Iodothyronines follow pattern of steroids except (1) a protein (thyroglobulin) acts as hormone precursor and as a large reservoir of stored hormone, as with peptide hormones; (2) half-lives in plasma are measured in days; and (3) receptors, i.e., major initial sites of interaction, are in the nucleus.

*For brevity, we designate peptide hormones (and growth factors) as well as catecholamines as "water-soluble hormones." and steroids, $1,25(\text{OH})_2$ vitamin D, and iodothyronines as "lipid-soluble hormones." The latter term is convenient but somewhat inaccurate since these hormones are amphiphilic, are very soluble in amphiphilic solvents such as alcohols, and only variably soluble in pure aqueous or pure lipid solvents.

(Roth and Grunfeld, 1985,

Figure B. MECHANISM OF ACTION OF PEPTIDE HORMONES AND CATECHOLAMINES

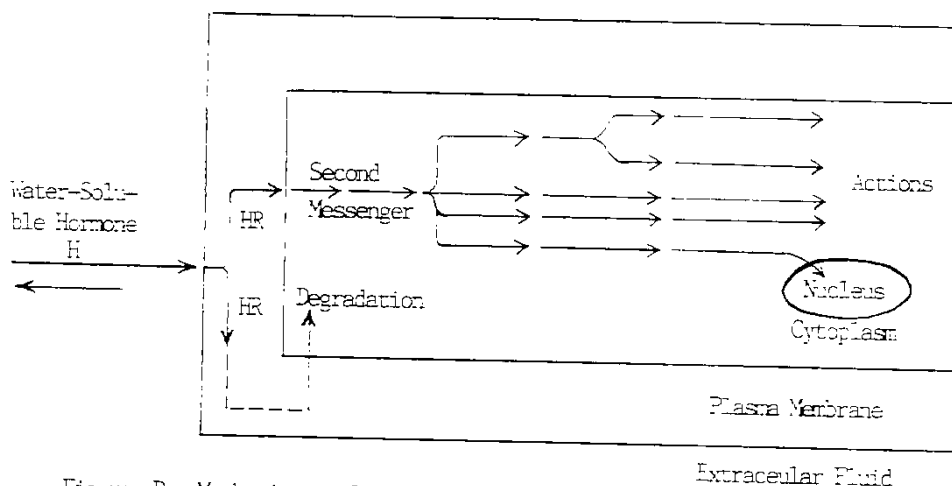


Figure B. Mechanisms of action of water-soluble hormones (peptides and catecholamines; abbreviated H), which interact reversibly with receptors on outer surface of target cell. Hormone-receptor complex (HR) interacts with one or more membrane components which, in absence of further participation of hormone, leads to stimulation of a common intracellular pathway (e.g., synthesis of cAMP and activation of protein kinase), which then activates multiple "branched" pathways within cell. Hormone need not enter cell for expression of hormone action; when it does enter, it is largely for purposes of degradation (broken line). Some effects of these hormones may be modifications of nuclear events, but these are not invariably present and represent only a minority of the events observed.

(MOTIL AND RICHFIELD, 1961)

The overall scheme by which peptide hormones and catecholamines activate target cells is shown in Fig B and Table B. The hormone (extracellular messenger) carries the signal from the secretory site to the cell surface. On the plasma membrane is a receptor that recognizes the hormone and binds it. The combination of hormone with receptor initiates a transmembrane message that results for most hormones in activation of the adenylate cyclase at the inner surface of the plasma membrane (Evans et al, 1964).