安徽教育出版社▶

REPRODUCTIVE PHARMACOLOGY 生殖藥理

顧芝萍・桑國衞・陳俊康 ・著

殖 CTIVE 五二年 00100

MOVE - 受害者・施力等・体

生殖藥理學

REPRODUCTIVE PHARMACOLOG

顧芝萍・桑國衞・陳俊康・著

GUZHIPING SANG GUO WEI CHEN

KANG



安徽教育出版社

责任编辑: 汪明华 封面设计: 牛 昕

生殖药理学

顾芝萍等 著 安徽教育出版社出版 (合肥市金寨路283号)

徽省4年4月发行 安徽新华印刷厂印刷

开本, 850×1168 1/32 印张, 11 字數, 300,000 1990年8月第1版 1990年8月第1次印刷 印数, 2,500

ISBN 7-5336-0505-5/G-986

平装本定价: 5.90元 精装本定价: 7.90元

PREFACE

The fields of pharmacology and fertility regulation have advanced independently in recent years. It is, therefore, appropriate that this volume appear, linking the two subjects.

As methods of fertility regulation were developed, based on oral or parenteral administration of systemic agents, the new field of reproductive pharmacology, emerged. Initially, in the 1960 s, this related to steroid hormones primarily. The ingestion of steroid hormones by women for fertility control dwarfed by comparison the use of steroids for all other purposes combined. This extensive use of steroids led to new methodology-first competitive

protein binding then radio-ligand assays to detect steroid blood levels with high degrees of sensitivity and specificity. As huge numbers of women became regular users of steroids, epidemiological studies revealed small changes in rare events, associations were disclosed that had not previously been suspected. This, in turn, prompted interest in issues such as steroid effects on carbohydrate metabolism, lipoproteins, clotting factors and other aspects of metabolism.

The discovery of the chemical structure of prostaglandins and later, hypothalamic releasing factors led to new areas of research in fertility regulation, and the pharmacology and pharmacokinetics of those agents. Once again, new methodologies emerged and new metabolic associations were determined.

With breathtaking speed, the biology of cell receptors for both steroid and protein reproductive hormones, appeared on the research scene and grew in importance. Within a few years of the discovery of progesterone receptors, compounds were synthesized which could successfully compete with the native hormone for receptor sites, and thereby act as anti-progestins. This pharmacologic effect has become the basis for the newest approach to fertility regulation in women.

Meanwhile, significant discoveries, more in the line of classical pharmacology, have been made pertaining to the regulation of male fertility. Thanks to research in China on gossypol, a natural plant product, an oral contraceptive for men could become a reality in the

near future. Methodology has also played a key role in this field. Now that sensitive methods are available to detect small levels of gossypol in blood and other tissues, understanding of the pharmacology of gossypol is beginning to move ahead rapidly.

This is the scientific terrain covered in this volume, prepared by Chinese scientists, each expert in the subject matter presented. This volume will be a valuable addition to the library of teachers, researchers and clinicians. It is comprehensive, upto-date and authoritative.

When one considers that more people in China use methods of fertility regulation than in any other country in the world, it is appropriate that a book on the pharmacology of these agents be written by Chinese experts.

> Sheldon J. Segal January 1989

近年来,药理学和生育调节在各自的领域中,都已经独立地取得了进展。本书把这两个学科结合起来,它的问世是很适时的。

随着人们发展了以全身作用的、 经口或胃肠道外给药为基础的生育调 节方法, 便开辟了生殖药理学的新领 域。最初,在60年代。这个新领域主 要涉及甾体激素, 妇女为计划生育而 服用甾体激素, 使得为其他一切目的 而应用甾体化合物的做法 都 相 形 见 拙。 甾体化名物的广泛应用, 导致了 检测血浓度的新方法的发现。这些方 法具有高度的敏感性和特异性。首先 是竞争性蛋白结合法, 以后是放射性 配基分析法。由于大量妇女经常使用 甾体化合物,流行病学研究发现了罕 见病例的轻微变化, 以及过去没有料 到的有关现象。因而, 使人们对下列 问题产生了浓厚的兴趣: 即甾体化合 物对糖代谢、脂蛋白、凝血因子及其 他代谢方面具有什么样的影响。

前列腺素化学结构的发现和随后的下丘脑释放因子化学结构的阐明。

开辟了生育调节研究的新领域,导致了对有关制剂的药理学和 药代动力学的研究,再次促进了新的方法学的产生以及与代谢 有关的发现。

对甾体和蛋白生殖的细胞受体生物学的研究以惊人的速度发展,并且日益显示出它的重要性。仅在发现孕激素受体的几年内,就合成了能够成功地与天然孕激素竞争受体位点的化合物,从而发挥出抗孕激素的作用。这种药理作用已经成为最新型的女性生育调节方法的基础。

同时,在经典药理学范围内,男性生育调节也取得了重要的发现。感谢中国科学家对一种天然植物产物棉酚的研究,它使得在不远的将来男用口服避孕药有可能成为现实。在这个领域内,方法学也起着关键性的作用。既然已经有了灵敏的方法以检测血液和其他组织中的微量棉酚,人们对棉酚的药理学作用的研究也正开始迅速地向前发展。

由中国科学家撰写的这本专著对以上内容作了科学的阐述,奉献了他们各自的专长。本书对教师、科研人员和临床医师很有价值,它内容丰富、材料新颖,有权威性。

中国使用 生育调 节方法的人数比 世界上 任何其他国家都多,由中国专家撰写生殖药理学专著很有意义。

希尔顿・西戈尔 1989年1月

前言

生殖药理学是一门新兴的边缘科学,它涉及生理、生化、药理、病理、内分泌、遗传、毒理和临床等多方面。本书注重这些学科知识的交叉和综合运用,深入、系统地介绍了生殖药理学的基础理论、研究方法及最

新进展,细致入微地阐述了影响生殖系统各环节的物质的化学结构、生物活性、作用机理,代谢过程及不良反应;本书还结合生殖药理学的基本原理和临床应用实践,较详细地介绍生育调控的原理和过程、发展避孕药的方向和手段、各类避孕药的研究现状及选择、临床应用研究的方法学、应用避孕药物的原则、评价方法和合理用药的要求。

本书共分十章,力求结构体系科学合理,反映作者从事生殖药理学研究几十年的知识和经验,体现我国生殖药理学的最新研究水平。本书填补了国内生殖药理学专著出版的空白。

在本书的出版过程中,得到了国内外同道的关注。国内很多同志玉成此事,给予了帮助和支持。安徽医科大学的徐叔云教授、马传庚副教授提出了许多宝贵意见,上海药物所的杨惠华、茅白勇和王月娥等帮助做了一些具体工作,浙江医学科学院的李晓峰、邵庆翔和张劲及上海计划生育研究所的宋诗参与个别章节的撰写,国外一些专家也多予鼓励,美国洛克菲勒基金委员会人口部主任希。西格尔博士深知本书精要及意义,热心推荐、欣然作序。谨此一并致谢。

生殖药理学是一门崭新的学科,本书论述中定有不妥之处。借此机会,就正于有道,指其瑕疵,匡其疏漏。

CONTENTS

Chapter 1

Neuro-endocrine regulation of reproduction

- §1 Neurotransmitters and hypothalamic hormones
- §2 Posterior pituitary and hypophyseal peptides
- §3 Gonadalhormones
- §4 Prostaglands
- §5 Inhibin and gonadal reproductive peptides (gona-docrinin)
- §6 Pineal gland

Chapter 2

Methods for research on reproductive pharmacology

- §1 Development and testing procedures of active antifertility agents
- §2 Assessment of antifertility activites
- §3 Measurement of endocrine activities
- §4 Application of radio-receptor assay in research on reproductive pharmacology
- §5 Reproductive toxicity test

Chapter 3

- Design and performance of clinical pharmacologic al studies for the assessment of contraceptive drugs
- §1 Development and clinical evaluation of contraceptives
- §2 Phase I clinical study—Pilot studies on the Pharmacology and tolerance of contraceptives in healthy volunteers
- §3 Phase I clinical trial—

 A.Preliminary controlled clinical trial of contraceptives

 B.Extended multi-centre clinical trial of contraceptives
- §4 Phase I clinical trial—Post-registration surveillance of contraceptives

Chapter 4

Steroidal contraceptives

- §1 Chemical structure of steroid contraceptives
- §2 Categories of steroid Contraceptives
- §3 Mechanism of action of steroid contraceptives
- §4 Adverse reactions and contraindication

Chapter 5

Metabolic effets of steroidal contraceptives and the possible correlation with the risk of neoplasia

§1 Effects of steroid contraceptives on carbohydrate metabolism

- §2 Effects of steroid contraceptives on lipids metabolism
- §3 Effects of steroid contraceptives on coagulation
- §4 Cardiovascular disease, hypertension and steroidal contraceptives
- §5 Risk of neoplasm
- §6 Hyperpolactinemia
- §7 Pituitary adenoma and steroidal contraceptives

Chapter 6

Clinical pharmacokinetics of steroidal contraceptives

- §1 Basic conception and terminology of pharmacokinetics
- §2 Pharmacokinetics of oral contraceptives
- §3 Pharmacokinetics of injectable and other nonparenteral contraceptive steroids

Chapter 7

Pre-clinical toxicological testing of contraceptive steroids

- §1 Historical review of toxicological studies on steroidal contraceptives
- §2 Comparative endocrinology of steroidal contraceptives
- §3 Comparative pharmacokinetics of steroidal contraceptives
- §4 Recommendations for testing of new contraceptive steroids in animal and other non-human pri-

mates

- §5 Initail toxicological study
- §6 Toxi cological study of multi-dose
- §7 Reproductive toxicity
- §8 Study of mutagenesis
- §9 Study of carcinogenesis
- §10 Sex of experimental an imals
- §11 New delivery systems containing existing steroidal contraceptires
- §12 New derivatives of steroid contraceptive
- §13 Toxicological test for combined steroidal ocntraceptives
- §14 Use of standard procedures in testing

Chapter 8

Clinical pharmacology of prostaglandins as a fertility regulation agent

- §1 Biosynthesis and metabolism of prostaglandins
- §2 Bological effects of prostagladin on reproductive systems
- §3 Clinical pharmacology of antifertility effect of prostaglandins

Chapter 9

Gonadotrophin releasing hormone (GnRH) and its analogues

- §1 Chemical structure and activities
- §2 GnRH analogues
- §3 Pharmacokinetics of GnRH and its analogues

§4 Clinical application of GnRH

Chapter 10

studies on the male contraceptives

- §1 Interference with endocrine regulation of reproduction
- §2 Antiandrogens
- §3 Antifertility compounds acting on seminiferous tubular
- §4 Disfunctional agents for male fertility control
- §5 Antifertility effects of sulphasalazine(SASP)
- §6 Gossypol

目 录

第-	-掌	生殖过	程的神经内分泌调控
	§ 1	神经递	质和下丘脑激素(1)
		1.1 神剣	圣元和神经递质(2)
		1.2 下月	丘脑的组成 ······(4)
		1.3 下臣	丘脑的激素(5)
		1.4 促性	生腺激素释放激素(6)
		1.4.1	GnRH的结构(6)
		1.4.2	GnRH的分布(6)
		1.4.3	GnRH的分泌(6)
		1.4.4	垂体前叶对GnRH的反应(7)
		1.4.5	GnRH的自身引发作用(8)
		1.4.6	控制GnRH分泌的两个中心(8)
		1.4.7	对LH和FSH分泌的区别控制(8)
	§ 2	垂体前	「叶激素(10)
	-	2.1 促性	生腺激素(10)
		2.1.1	化学结构和性质(11)
		2.1.2	生物合成和储藏(14)
		2.1.3	分泌的调控(14)
		2.1.4	血浆促性腺激素浓度和生理图象(15)
		2.1.5	对卵巢和睾丸的作用(17)
		2.1.6	雌激素合成的两种细胞学说(18)