# Contents

#### **CHAPTER 1**

## Some Aspects of the History of Local Anesthesia

L. D. VANDAM $\ldots$	•	·	•	٠	•	1
A. Introduction					•	1
B. Freud, Koller and the Early History of Cocaine						2
C. Structure and Synthesis of Local Anesthetics					•	4
D. Epinephrine and Local Anesthesia					•	6
E. Toxicity of Local Anesthetics				٠		9
F. The Nervous Impulse and the Action of Local Anesthetics						12
G. Pharmacokinetics of Local Anesthetics						15
H. Summary and Conclusions				•		17
References		·	·	•	•	18

The	e Action of Local Anesthetics on Ion Channels of Excitable Tissues	
G. I	R. STRICHARTZ and J. M. RITCHIE. With 7 Figures	21
А.	Introduction	21
B.	Physiological Basis of Generation of the Action Potential	21
	I. Role of Ion Channels	21
	II. Kinetic Properties of Sodium Channels	22
	III. Gating Currents	24
	IV. Pharmacological Dimensions of the Sodium Channel.	25
C.	The Action of Local Anesthetics on Sodium Channels	26
	I. Distribution of Local Anesthetics and the Mechanism	
	of Their Blocking Action	26
	II. The Modulated Receptor Hypothesis:	
	Past and Present Formulations	28
D.	Current Questions in Local Anesthetic Action	32
	I. Location of Local Anesthetic Binding Site(s)	
	in the Sodium Channel	32
	II. Factors that Determine Rates of Action and Potencies	
	of Local Anesthetics	33
	III. The Number and Nature of Local Anesthetic Binding Sites	34
E.	New Kinds of Local Anesthetic Agents	43
	-	



F.	Effects of I	Loca	1 A	۱ne	est	he	tic	s c	n	Pc	ota	ssi	un	1 (	Ch	an	ne	ls					45
G.	Conclusion											•											46
Ref	erences												•		•								47

1

## CHAPTER 3

Structural Elements which Determine Local Anesthetic Activity
K. R. COURTNEY and G. R. STRICHARTZ. With 12 Figures 5
A. Introduction
I. Scope of Review and Methodology
II. Measurements of Anesthetic Action
B. Structure and Physico-Chemical Properties of Local Anesthetics 6
C. Resolution of Structural Contributions to Potency
I. Aromatic Groups
II. Amide, Ester, and Ether Bonds
III. Intermediate Alkyl Chain
IV. Terminal Amine
V. Stereoisomers
VI. Onset and Duration of Action
D. Comparisons of Nerve Blocking Actions with Antiarrhythmic Actions
of Local Anesthetics 7
L Sensitivity of Nerve Versus Muscle
II Different Inactivation Gating in Nerve and Heart 7
III Factors Determining Potency in Heart
IV Relevance to Cardiotoxicity 8
V Importance of Intermediate Open and Inactive Channel Blocking 8
F Models for Local Anesthetic Recentors
L. Models for Local Anesthetic Action
I. Rifetic Models of Local Ancesticite Action
II. Invsite-Chemical Models
IV Molecular Substrate for the Block Decovery Process
Poforences

Me	chanisms of Differential Nerve Block
S. A	A. RAYMOND and A. J. GISSEN. With 13 Figures
Α.	Introduction
B.	Historical Discussion
	I. Differential Tonic Block
	II. Origins of the Dominant Paradigm
	III. Synthesis: The Size Principle
C.	Confirmations, Extensions, Clarifications, and Contradictions 103
	I. Confirmation and Extension of the Size Principle

Contents

II. Contradictions of the Size Principle; Importa	ano	ce o	of 4	Ad	di	tio	na	1	
Factors	•				•			•	116
D. Summary and Conclusion						•			150
I. The Notion of Functional Specificity	•				•				151
II. A Distributed Model of Conduction Safety	•				•		•		151
References	•			·	•	•	·	•	155

## CHAPTER 5

1

<b>Pharmacokinetics of Local Anesthetics</b> G. R. ARTHUR, With 5 Figures				. 1	65
A Introduction	•••	•••	• •	1	65
A. Introduction	$D_1$	 aad	• •	. 1	05
b. Factors Affecting the Interpretation of Local Affectieut	) DK	ood			
Concentrations	•••	• •	• •	. 1	65
I. Units of Expression		• •		. 1	65
II. Sampling Site				. 1	66
III. Plasma Protein Binding				. 1	67
C. Metabolism				. 1	68
I Ester Type Local Anesthetics	-			1	68
II Amide Type Local Anesthetics	•••	•••	• •	. 1	60
D. Dharmanalization in Man	• •	• •	• •	. 1	77
D. Pharmacokinetics in Man	•••	•••	• •	. 1	14
E. Factors Affecting Pharmacokinetics of Local Anesthetic	S.	• •	• •	. 1	74
I. Lung Uptake of Local Anesthetics		• •		. 1	74
II. Age				. 1	75
III. Other Drugs				. 1	77
IV. Disease				. 1	78
V Other Factors				1	79
E Pharmacokinetics in Experimental Animals	•••	• •	• •	1	۷'n
P. Fharmatokineties in Experimental Annuals	• •	• •	• •	. 1	00
Kelerences	•••	• •	• •	. 1	ð2

<b>Coxicity and Systemic Effects of Local Anesthetic Agents</b>	
B. G. COVINO. With 3 Figures	187
A. Effects on the Central Nervous System	187
B. Effects on the Cardiovascular System	193
I. Cardiac Effects	194
II. Peripheral Vascular Effects	197
C. Effects on the Neuromuscular Junction	202
D. Miscellaneous Effects	203
E. Other Toxicological Effects	204
F. Treatment of Systemic Toxicity	205
G. Local Tissue Toxicity	206
H. Summary	208
References	209

#### **CHAPTER 7**

The Role of Local Anesthetic Effects in the Actions of Antiarrhythmic Drugs
G. A. GINTANT and B. F. HOFFMAN. With 10 Figures
A. Introduction
B. Electrophysiology of Cardiac Fibers
I. Description of the Cardiac Action Potential
II. Fast Responses and Slow Responses
III. Excitability, Refractoriness, and Responsiveness
C. The Effects of Local Anesthetics on Cardiac Fibers
I. Effects on Fast Inward Sodium Current
II. Effects on Action Potential Duration
III. Effects on Phase 4 Depolarization and Normal Automaticity 231
D. Antiarrhythmic Effects of Local Anesthetic Agents
I. Classification of Arrhythmias
II. Arrhythmias Due to Altered Impulse Initiation
III. Reentrant Rhythms
E. Conclusion
References

Central Effects of Local Anesthetic Agents
J. M. GARFIELD and L. GUGINO. With 2 Figures
A. Introduction
B. Routes of Entry of Local Anesthetic Agents into the CNS 253
C. Behavioral Pharmacology of Local Anesthetic Agents
I. Animal Studies of Locomotor Activity, Behavior
and Correlative Neural Activity
II. Effects of Local Anesthetics on Conditioned Behavior
III. Behavioral Effects of Local Anesthetics in Man
D. Effects of Local Anesthetics on Electrical Activity of the Brain 264
I. The Convulsant Properties of Local Anesthesia
E. Anticonvulsant Properties of Local Anesthetics
F. Temporal and Spatial Effects of Local Anesthetics at Regional CNS Sites 270
I. The Amygdaloid Complex as the Initial CNS Target of Local
Anesthetics
II. Anatomy and Function of the Amygdaloid Complex
III. Other CNS Structures Affected by Local Anesthetics
G. The Mechanisms Underlying Local Anesthetic-Induced Seizures 276
I. Local Anesthetic Induced Disinhibition of Neuronal Pathways . 276
II. The Interplay of Local Anesthetics and Putative Neurotransmitters
and Neuromodulators
H. Central Nervous System Metabolic Effects of Local Anesthetics 278
I. Summary
References
Subject Index