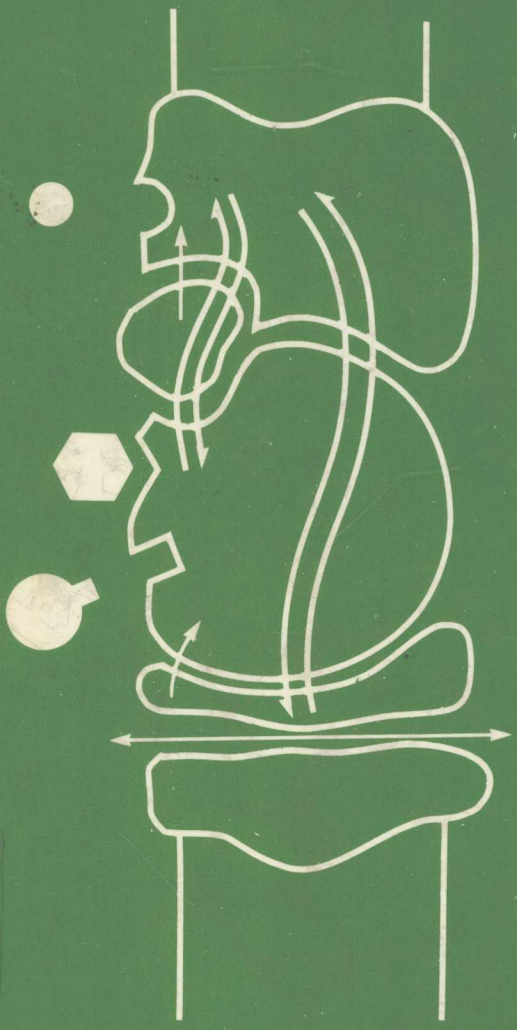
Pharmacology of Benzodiazepines



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Pharmacology of Benzodiazepines

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Abbreviations

ACh = acetylcholine
ACTH = corticotrophic hormone
AD = antidepressant
α_1-AGP = acid glycoprotein
(A&H)I = (Apnea and Hypopnea) Index
AMK = N-acetyl-5-methoxy kynurenamine
AMP = adenosine monophosphate
API = atmospheric pressure ionization
β-AR = β-adrenergic receptor(s)
ARAS = ascending reticular activity system
ASDC = Association of Sleep Disorder Centers
ATP = adenosine triphosphate
AUC = area under the curve

BR = benzodiazepine receptor(s)
BZ = benzodiazepine(s)
βCCE = ethyl-β-carboline-3-carboxylate
βCCM = methyl-β-carboline-3-carboxylate
βCCP = propyl-β-carboline-3-carboxylate
CDZ = chlordiazepoxide
CHAPS = 3[(3-cholamidopropyl) dimethyl-ammonio]propane sulfonate
CHEB = 5-ethyl-5-(2-cyclohexyl-idenethyl)barbituric acid
CI = chemical ionization
CLB = clobazam
CLP = clorazepate dipotassium
CNS = central nervous system
COPD = chronic obstructive pulmonary disease
CPZ = chlorpromazine
CZP = clonazepam

DBI = benzodiazepine binding inhibitor
DE = detergent receptor extract
DHA = dihydroalprenolol
DHP = dihydropicrotoxin
DIMS = Disorders of Maintaining Sleep
DMBB = dimethylbutyl barbituric acid
DMCM = methyl-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate
DMDZ = desmethyldiazepam
DME = dropping mercury electrode
DPP = differential pulse polarography
DRP = dorsal root potential(s)
DZP = diazepam

EC = electron capture (detector)
ECG = electrocardiograph
ECS = electroconvulsive shock (therapy)
EDTA = ethylenediamine tetra-acetic acid
EEG = electroencephalogram
EGTA = ethyleneglycol-bis(β-aminoethyl ether)-N,N'-tetra-acetic acid
EMG = electromyogram
EOG = electro-oculogram
ES = electroshock seizures

FDA = F.D.A. = (U.S.) Food and Drug Administration
FFA = free fatty acids
FLU = flunitrazepam
FMN = FLU

GABA = γ-aminobutyric acid
GC-MS = gas chromatography/mass spectroscopy
GDP = guanosine diphosphate
GLC = gas/liquid chromatography
GMP = guanosine monophosphate
GTP = guanosine triphosphate

HDRS = Hamilton Depression Rating Scale
3-HMC = 3-hydroxymethyl-β-carboline
HPF = hippocampal formation
HPLC = high performance (or pressure) liquid chromatography
HPTLC = high performance thin-layer chromatography

i.c.v. = intracerebroventricularly
IGV = isoguvacine
ipsps = inhibitory postsynaptic potentials

K = kindled

LSD = lysergic acid diethylamide
LZP = lorazepam

MED = minimal effective dose
MES = maximal electroshock seizure
MMPI = Minnesota Multiphasic Personality Inventory
MS = mass spectrometry
MSLT = Multiple Sleep Latency Test
MTZ = metrazol
MUA = multiunit activity
MW = molecular weight(s)

NCI = negative chemical ionization
NDD = N-desmethyldiazepam
N/P-D = nitrogen/phosphorus detector

OTC = over-the-counter

PAGE = polyacrylamide gel electrophoresis
PCI = positive chemical ionization
PCPA = p-chlorophenylalanine
PMSF = phenylmethyl sulfonyl fluoride
PrCC = propyl β-carboline-3-carboxylate
P4S = piperidine-4-sulfonate
PTZ = pentylenetetrazole = pentetrazole

QNB = quinuclidinyl benzilate

REM = rapid eye movement (sleep)
RIA = radioimmuno assay

SCN = thiocyanate (ion)
SDS = sodium dodecyl sulfate
SE = salt soluble receptor extract
SSD = Shock-induced Suppression of Drinking

TBAOH = tetrabutyl-ammonium hydroxide
THIP = 4,5,6,7-tetrahydroisoxazolo-4,5c-pyridine-3-ol
TMS = trimethyl silyl
TPZ = triazolopyridazine(s)
TRS = thirsty rat conflict

WCOT = wall-coated open tubular

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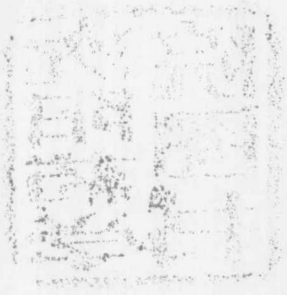

1

Introduction

Historically, the benzodiazepines have been among the most widely prescribed of all drugs. The reasons for this popularity are complex and involve several factors including: unequivocal therapeutic efficacy, the ubiquitous nature of anxiety and sleep disorders, relative safety compared to other minor tranquilizers, effective marketing by pharmaceutical companies, and their rather broad spectrum of pharmacologic activity. Like most psychotropic agents the benzodiazepines were discovered by a combination of serendipity and astute empericism catalyzed by a close working relationship between the medicinal chemist and pharmacologist. Over the past several years many refinements in their clinical use including better assessment of their pharmacokinetics and metabolism and particularly as these relate to side effects, toxicity, tolerance and dependence have been made. The most important recent achievements, however, involve the rapid explosion in basic biochemical information concerning their mechanism(s) of action. These studies, which have been summarized to a great extent in this book, open up new areas not only in psychopharmacology as a clinical discipline, but in our basic understanding of the nervous system, especially what appears to be major inhibitory and excitatory brain mechanisms. We now know, for example, that the brain contains specific receptor or recognition sites for the benzodiazepines and that these receptors are tightly coupled to other regulatory units including the GABA and barbiturate recognition sites. We suspect that a variety of chemically-unrelated minor tranquilizers may produce their pharmacological effects through this supramolecular receptor "complex." Perhaps the most exciting implications of these findings concern the role of this supramolecular receptor "complex" in mediating human anxiety. Although this possibility has been speculated on previously, it was not until the discovery of receptor ligands which antagonize the benzodiazepines, and others that produce opposing pharmacological effects to those of the benzodiazepines, that this hypothesis