Contents

Pref Autl		xi xiii
	pter 1 neostasis of Dopamine	1
1.1	INTRODUCTION	1
1.2	BIOSYNTHETIC ENZYMES	2
1.2.1	Tyrosine hydroxylase	3
	Dopa decarboxylase	5
1.2.3	Dopamine beta-hydroxylase and phenylethanolamine- <i>N</i> -methyltransferase	6
1.3	METABOLIC ENZYMES	7
1.3.1		8
	Catechol-O-methyltransferase	9
1.3.3	Glucuronosyltransferases and sulfotransferases	10
1.4	MEMBRANE AND VESICULAR	
1 4 1	TRANSPORTERS	12
1.4.1	Transporters of monoamine neurotransmitters The dopamine transporter	12 14
	Pharmacology of DAT	15
	DAT-deficient mice	16
1.4.5	Vesicular monoamine transporters	16
1.4.6	Organic cation transporters and plasma membrane monoamine transporters	18
1.5 1.5.1	STORAGE, RELEASE, AND REUPTAKE Functional coupling between DA synthesis	19
1 5 7	and storage	19 20
	Characteristics of synaptic vs. secretory vesicles Mechanism of exocytosis	22
	ERENCES	24
Cha	pter 2	
	amine Receptors, Signaling	
Path	ways, and Drugs	27
2.1	INTRODUCTION	27
2.2	DOPAMINE RECEPTORS: STRUCTURE-FUNCTION	
	RELATIONSHIP	28
2.2.1	Overview of G protein-coupled receptors (GPCR)	28
2.2.2		29
772	of the GPCRs Coupling of the GPCRs to G proteins	29 30
	General characteristics and regulation	50
	of the DARs	33

i i	2.2.5	Specific properties and brain distribution of D1-like receptors	36
L	2.2.6	Specific properties and brain distribution of D2-like receptors	38
	2.2.7	DAR oligomerization, desensitization, and constitutive activity	40
l	2.3		
2		NONCANONICAL SIGNALING BY DAR SUBTYPES	42
3	2.3.1	The consequences of DAR coupling to G proteins	42
5	2.3.2	The adenylate cyclase/cAMP/PKA signaling	43
,	233	pathway Cross-talk of multiple signaling pathways	43 44
3		Role of the cGMP pathway	45
)		DAR AGONISTS AND ANTAGONISTS	46
)		Overview of DAR-selective ligands	46
		D2R-altering drugs	47
2		Atypical antipsychotics	48
2		Drug selectivity Peripheral dopaminergic altering drugs	48 49
ł			47
	2.5	DOPAMINE RECEPTOR KNOCKOUT MICE	50
5	251	Phenotypes of individual DAR-KO mice	50
,		D2R deletion and pituitary functions	51
, ,	2.6	SYNOPSIS	51
	REFE	ERENCES	52
)			
	Cha	pter 3	
	Dist	ribution and Characteristics	
	of B	rain Dopamine	55
	3.1	INTRODUCTION	55
	3.2	NORADRENERGIC AND ADRENERGIC NEURONS	56
	3.2.1	Historical perspectives	56
	3.2.2	Distribution and major functions of the brain noradrenergic neurons	58
	3.2.3	Distribution and major functions of the brain adrenergic neurons	59
	3.3	DOPAMINERGIC NEURONS	60
	3.3.1	Classification of the brain dopaminergic neurons	60
	3.3.2	Mesocortical, mesolimbic, and nigrostriatal dopaminergic pathways	61
	333	Retinal olfactory and nineal donaminergic	

3.3.3 Retinal, olfactory, and pineal dopaminergic neurons

CONTENTS

3.4	THE HYPOTHALAMUS: STRUCTURE AND FUNCTIONS	65
3.4.1	Anatomy of the hypothalamus	65
3.4.2	The hypothalamic nuclei: Locations	
3.4.3	and major neuroendocrine functions Catecholaminergic innervation of the	66
5.4.5	hypothalamus	70
3.5	THE HYPOTHALAMO-PITUITARY	
	COMPLEX: NEURAL AND VASCULAR CONNECTIONS	71
3.5.1	Functional anatomy of the	, 1
	hypothalamo-pituitary complex	71
3.5.2	Embryonic development and gross anatomy of the pituitary gland	72
3.5.3	The hypothalamo-pituitary complex: Neural connections and DA concentrations	73
3.5.4	The hypothalamo-pituitary complex:	
	Vascular connections and DA levels in portal blood	75
~ <	•	
3.6	SYNOPSIS	78
REF	ERENCES	78
Cha	pter 4	
	ocrine Functions of Brain	
	pamine	81
	INTRODUCTION	81
4.2	CIRCADIAN RHYTHMS	82
	Circadian rhythms and their impact on health and disease	82
4.2.2	The neurocircuitry that controls circadian	
	rhythms and the role of dopamine	84
	Dopamine and retinal rhythmicity	84
	Dopamine and the suprachiasmatic nucleus	85
4.2.5	Effects of DA on the pineal: Regulation of melatonin synthesis and release	86
4.2.6	Effects of dopamine on the circadian rhythms	0.0
	of circulating hormones	88
4.3		
	RESPONSE	90
4.3.1	Time-related, multi-facetted activation of the stress response	90
4.3.2	2 Central dopamine and the stress response: Interactions with the HPA axis	92
4.3.3	3 Circulating dopamine and the stress response	94
	Dopamine and the stress response: Interaction with sexually dimorphic hormones	s 95
4.4	FOOD INTAKE AND METABOLIC	
1.1	HOMEOSTASIS	98
4.4.	Control of body weight and the consequences of dysregulation of food intake	98
4.4.	2 The hypothalamus: A major relay station	
	that controls feeding behavior	98

4.4.3	Leptin, a major suppressor of appetite
1 1 1	

4.4.4 Pancreatic hormones: Insulin and amylin

65	4.4.5	Gastrointestinal hormones involved in the regulation of food intake	104
65	4.4.6	Involvement of dopamine in the control	
66		of feeding behavior	105
	4.5	NEUROENDOCRINE REGULATION OF REPRODUCTION AND SEXUAL/	
70		MATERNAL BEHAVIOR	107
	4.5.1	Synthesis of GnRH, origin and migration of GnRH neurons, and genetic dysfunctions	108
71	4.5.2	Kisspeptins, GnRH pulsatility, and the role of dopamine	108
71	4.5.3	Reproductive functions of PRL and reciprocal interactions with dopamine	110
72	4.5.4		112
73	4.5.5	Regulation of sexual and maternal behavior	112
	4.6	SYNOPSIS	115
75	REFE	ERENCES	115
78			
78		pter 5 ulation of the Pituitary Gland	
		Dopamine	119
	5.1	INTRODUCTION	119
81	5.2	NEURAL LOBE HORMONES:	
81	5 3 1	VASOPRESSIN AND OXYTOCIN	119
82	5.2.1	Ontogeny and composition of the posterior pituitary (neurointermediate lobe)	119
82	5.2.2	Synthesis, transport, and processing of the neurohypophysial hormones	121
84	5.2.3	Vasopressin: Receptors, functions, and regulation	123
84	5.2.4	Oxytocin: Receptors, physiology, and regulation	124
85	5.2.5	Effects of dopamine on the neurohypophysial hormones	126
86	5.3	INTERMEDIATE LOBE HORMONES:	
88	5.3.1	β-ENDORPHIN AND α-MSH Structure, innervation and regulation	127
		of the intermediate lobe	127
90		Synthesis and processing of POMC and its derivatives	128
90	5.3.3	Regulation of intermediate lobe hormones by dopamine	128
92	5.4	COMPOSITION AND ONTOGENY	
94	- 4 1	OF THE ANTERIOR PITUITARY	129
95	5.4.1	Anterior pituitary structure, cell types, and dopamine receptors	129
	5.4.2	Ontogeny of anterior pituitary cell lineage	131
98	5.5	SOMATOLACTOGENIC HORMONES: PRL AND GH	133
98	5.5.1	Structure and properties of somatotrophs	
98	5.5.2	and lactotrophs PRL: Structure, synthesis, regulation,	134
101		and functions	134
102	5.5.3	3 GH: Structure, synthesis, and regulation	138

5.6	REPRODUCTIVE HORMONES: LH AND FSH	141
5.6.1		142
5.6.2	GnRH and the GnRH receptor	143
5.6.3	FSH: Structure, synthesis, regulation and functions	144
5.6.4	LH: Structure, synthesis, regulation, and functions	145
5.6.5	Regulation of the hypothalamo-pituitary- gonadal axis by dopamine	146
5.7	STRESS AND METABOLIC HORMONES: ACTH AND TSH	147
5.7.1	Corticotrophs and ACTH	148
	Major disorders associated with dysfunctions of the HPA axis	149
5.7.3	Involvement of dopamine in the regulation of the HPA axis	151
	Thyrotrophs and TSH	151
	Disorders of the hypothalamo-pituitary- thyroid axis	153
5.7.6	Involvement of dopamine in the regulation of the HPT axis	154
5.8	SYNOPSIS	154
REF	ERENCES	154
	pter 6	
	ibutes of Peripheral Dopamine Dopamine Receptors	159
	-	
6.1	INTRODUCTION	159
6.2	SOURCES OF CIRCULATING DOPAMINE	159
6.2.1	Biosynthesis, storage, release, and metabolism of peripheral catecholamines	150
622	The origin of circulating dopamine	159 160
6.2.3		100
	dopamine	162
6.3	UNIQUE CHARACTERISTICS	162
6.3.1	OF DOPAMINE SULFATE Sulfoconjugation of peripheral dopamine	163
6.3.2		164
		101
6.4	DOPAMINE RECEPTORS IN THE CARDIOVASCULAR, PULMONARY,	
6.4.1	AND RENAL SYSTEMS The cardiovascular and renal systems	166
6.4.1	The respiratory system	167
		107
6.5	DOPAMINE RECEPTORS IN THE DIGESTIVE SYSTEM AND IN ORGANS THAT REGULATE	

6.6	DOPAMINE RECEPTORS IN HEMATOPOIETIC AND IMMUNE		
	SYSTEMS	172	
6.6.1	Dopamine receptors in lymphoid organs	172	
6.6.2			
	lymphocytes	173	
6.7	DOPAMINE RECEPTORS IN SKIN		
	AND BONES	174	
6.7.1		174	
6.7.2	Dopamine receptors in different skin	174	
1	components	174	
	Bone structure	175	
	Dopamine receptors in bone cells	175	
6.8	DOPAMINE RECEPTORS IN MALE ANI		
	FEMALE REPRODUCTIVE SYSTEMS	176	
6.8.1	· · · · · · · · · · · · · · · · · · ·	176	
6.8.2	1 5	176	
6.8.3	The female reproductive system	177	
6.9	SYNOPSIS	178	
REF	ERENCES	179	
Cha	pter 7		
	al, Cardiovascular, and		
	nonary Functions of Dopamine	183	
7.1	INTRODUCTION	183	
		100	
7.2	RENAL FLUID HEMODYNAMICS	102	
721	AND HYPERTENSION	183	
7.2.1	Kidney development and gross anatomy The nephron: Structure-function relationship	183 185	
	Urine formation and composition	185	
7.2.3		100	
1.2.4	by the kidney	187	
725	Dopamine: Roles in essential hypertension		
7.2.0	and renal hemodynamics	189	
7.3	RENAL NATRIURESIS,		
	OXIDATIVE STRESS, AND DIABETIC		
	NEPHROPATHY	192	
7.3.1			
	electrolyte balance and osmolarity	192	
7.3.2	Endocrine regulation of natriuresis by the kidney	193	
722		193	
7.3.3			
	Renal dopamine and oxidative stress	195	
	Dopamine and diabetic nephropathy	195	
	CARDIAC FUNCTIONS	197	
7.4.1	1 5	197	
7.4.2			
1.1.2	nathonhysiological conditions	198	
	pathophysiological conditions	198	
7.5	BLOOD PRESSURE REGULATION		
		198 199 199	

6.5.1 The digestive system6.5.2 Metabolic regulation

METABOLISM

7.5.2 Dopamine and angiogenesis

CONTENTS

7.6	RESPIRATION AND OXYGEN-SENSING	202
7.6.1	Dopamine homeostasis in the upper respiratory tract	203
7.6.2	Dopamine involvement in upper airway pathophysiology	204
7.6.3	Dopamine and carotid body functions	204
7.7	PULMONARY VENTILATION	
	AND PATHOPHYSIOLOGY	205
7.7.1	De novo dopamine synthesis in the lung	206
	Actions of dopamine in the lung	206
7.8	SYNOPSIS	208
REFE	RENCES	209
Cha	pter 8	
Dige	stive and Metabolic Actions	
of D	opamine	213
8.1	INTRODUCTION	213
8.2		
	MOTILITY	214
	Pharynx and esophagus	214
	Stomach and duodenum	216 218
	Small and large intestine	210
8.3	GASTROINTESTINAL SYSTEM:	210
831	DIGESTIVE FUNCTIONS Salivary glands	219 220
	The stomach	220
8.3.3		221
	pancreas and gall bladder	222
	Small and large intestines	223
8.3.5	Enteric dopaminergic system and the	224
	gut microbiome	224
8.4	ORGANS THAT REGULATE	
	METABOLISM: PANCREAS, ADIPOSE TISSUE, AND LIVER	226
8.4.1	Endocrine pancreas and glucose	220
	metabolism	227
	Adipose tissue	228
8.4.3	The liver	231
8.5		
	ADVERSE EFFECTS OF	62.22
0 5 1	ANTIPSYCHOTIC DRUGS	233
	Dopamine, diabetes, and obesity	233
0.3.2	Adverse effects of antipsychotic medication on body weight and	
	metabolic syndrome	234
8.6	SYNOPSIS	235
REF	ERENCES	236

	mine in the Immune and atopoietic Systems	241
9.1	INTRODUCTION	24
9.2	CELLS DERIVED FROM THE	
	LYMPHOID LINEAGE	24
9.2.1	T cells, B cells, and NK cells	24
9.2.2	The dopaminergic system in lymphocytes and NK cells	24
9.3	CELLS DERIVED FROM	
	THE MYELOID LINEAGE	24
9.3.1	The dopaminergic system in erythrocytes	24
023	and platelets	24
9.3.2	The dopaminergic system in various leucocyte subtypes	24
0.4		
9.4	AUTOIMMUNE DISEASES AND NEUROPSYCHIATRIC DISORDERS	25
9.4.1	Dopamine and autoimmune diseases	25
9.4.2	Dopamine, immune system, and	
	neurological disorders	25
9.4.3	Dopamine, immune system, and	25
	psychiatric disorders	25
9.5	ENDOTHELIAL CELLS,	
	ANGIOGENESIS, AND COAGULATION	
9.5.1	Endothelial cells and dopamine	25
9.5.2	Angiogenesis and dopamine	25
9.5.3	Blood clotting and the coagulation cascade	26
9.6	INFLAMMATION AND ALLERGIC	
~	REACTIONS	26
9.6.1	Inflammation and dopamine	26
9.7	SYNOPSIS	26
REFE	RENCES	26
Chap	oter 10	
	llation of Reproduction	~ 7
-	opamine	27
10.1	INTRODUCTION	27
10.2	SEX DETERMINATION AND SEXUAL DIFFERENTIATION OF THE BRAIN	27
10.2.1	Genetic and hormonal components of sexual determination and differentiation	2
10.2.2	of sexual differentiation in the brain	2
10.2.3	program by endocrine disruptors	2
1024	Association of donamine with sevual	

10.2.4 Association of dopamine with sexual differentiation in the brain

10.2.5 Gender identity and sexual preference

277

278

10.3	HYPOTHALAMO–PITUITARY REGULATION OF REPRODUCTION IN BOTH SEXES	27
10.3.1	Common features of the central control	
10.3.2	of reproduction Involvement of dopamine in hypothalamic	27 28
10.3.3	control of reproduction and sex behavior Involvement of dopamine in the control of reproduction by the pituitary	28
10.3.4	Dopamine indirectly regulates reproductive functions through the control of prolactin	28
10.4	MALE REPRODUCTION: TESTES	
10 4 1	AND THE GENITAL TRACT	28
10.4.1 10.4.2	The male gonads: Spermatogenesis The male gonads: Steroidogenesis and	28 28
10.4.3	protein hormone production Involvement of dopamine with testicular functions	28
10.4.4	The male genital tract	28 28
10.5	FEMALE REPRODUCTION: OVARIES AND GENITAL TRACT	28
10.5.1	Unique characteristics of female reproduction	28
10.5.2	The female gonads: Oogenesis, folliculogenesis, and ovulation	28
10.5.3	The female gonads: Steroidogenesis	29
10.5.4	Involvement of dopamine with ovarian functions	29
10.5.5	The female genital tract	29
10.6	FERTILIZATION, PREGNANCY, AND FETAL DEVELOPMENT	298
10.6.1	Overview of conception, pregnancy, and embryonic development	29
10.6.2	Fertilization	29
10.6.3	Blastocyst transport and implantation	30
10.6.4	Endocrine functions of the placenta	30.
10.6.5	L-Dopa and dopamine levels in different compartments of pregnancy	30.
10.6.6	Development of the fetal reproductive organs	30
10.7	PARTURITION AND LACTATION	300
10.7.1	The process of parturition	30
10.7.2	Hormonal regulation of lactation	30
10.8	NEONATAL DEVELOPMENT,	201
10.8.1	PUBERTY, AND AGING The reproductive axis during the neonatal and prepubertal periods	30 8
10.8.2	Hormonal control of puberty and disorders of puberty	30
10.8.3	Aging of the reproductive system	31
10.9	SYNOPSIS	31
REFE	RENCES	31

279	Actio	oter 11 ons of Dopamine on the Skin the Skeleton	317
279	11.1	INTRODUCTION	317
280	11.2	SKIN STRUCTURE AND WOUND HEALING	318
281	11.2.1 11.2.2	Overview of skin structure	318 320
281	11.2.3 11.2.4	Role of dopamine in wound healing Polydopamine nanopolymers used for drug delivery in	321
283		wound healing	323
284 285	11.3	MELANOGENESIS	325
286	11.3.1	Overview of skin pigmentation and melanogenesis	325
287	11.3.2 11.3.3	Selected disorders of pigmentation Role of dopamine in skin pigmentation and its disorders	328 329
288	11.4	SWEATING	330
288	11.4.1	Overview of sweating, apocrine, and eccrine glands	330
289	11.4.2	Dopamine and sweating	330
293	11.5 11.5.1	HAIR GROWTH Overview of hair growth and its hormonal	332
293 294	11.5.2	regulation Role of dopamine in hair growth	332 333
298	11.6	THE SKELETON AND BONE REMODELING	334
298	11.6.1	Overview of the skeleton and bone remodeling	334
299 301	11.6.2	Involvement of dopamine in bone homeostasis	336
302	11.7 11.7.1	JOINTS, BONES, AND MUSCLES Overview of joints and muscles	337 337
303	11.7.2	Involvement of dopamine in muscle disorders	338
305 306	11.7.3	Involvement of dopamine in bone and synovial joint disorders	340
306	11.8	SYNOPSIS	342
307	REFE	RENCES	342
308	Chap	oter 12	
308	Dopa	amine and Tumorigenesis in oductive Tissues	345
309 310	12.1	INTRODUCTION	345
311	12.2	PITUITARY TUMORS	346
311	12.2.1	Prevalence, classification, and molecular characterization of pituitary tumors	346

CONTENTS

12.2.2	Prolactinomas and dopamine: Pathogenesis and treatments	34
12.2.3	Dopamine and other pituitary adenomas subtypes	35
12.3	BREAST CANCER	352
12.3.1	Prevalence, classification, and molecular characterization of breast cancer	352
12.3.2	Chemotherapy and immunotherapy in breast cancer	354
12.3.3	Hormone and targeted therapies in breast cancer	355
12.3.4	DARPP: A dopamine-regulated phosphatase involved in tumorigenesis	358
12.3.5	D1R expression and actions in breast cancer	359
12.4	OVARIAN CANCER	362
12.4.1	Characteristics of ovarian cancer	362
12.4.2	Involvement of dopamine in ovarian cancer	363
12.5	ENDOMETRIAL AND CERVICAL CANCER	365
12.6	PROSTATE AND TESTICULAR	
	CANCER	366
12.6.1	Characteristics of prostate cancer	366
12.6.2		366
12.6.3	Testicular cancer	367
12.7	SYNOPSIS	368
REFE	RENCES	368
	oter 13 vement of Dopamine with	
	ous Cancers	373
	INTRODUCTION	373

13.2	HEMATOLOGICAL MALIGNANCIES	
13.2.1	Prevalence and classification of	
	hematological malignancies	
13.2.2	Attributes and classification of leukemias	

347	13.2.3 13.2.4	Involvement of dopamine in leukemias Association of dopamine with lymphomas	375 376
517			376
351	13.3	GASTROINTESTINAL-RELATED	270
352	13.3.1	CANCERS Dopamine and overall incidence of GI	378
	13.3.1	malignancies	378
352	13.3.2	Gastric cancer	379
354	13.3.3	Colorectal cancer	380
	13.3.4	Liver cancer	382
355	13.3.5	Pancreatic cancer	383
358	13.4	LUNG, KIDNEY, AND BLADDER CANCERS	384
	13.4.1	Lung cancer and dopamine	384
359	13.4.2	Kidney and bladder cancer	386
362	13.5	CANCERS OF THE SKIN	386
362	13.5.1	Prevalence and attributes of skin cancer	386
363	13.5.2	Dopamine and melanoma	387
365	13.6 13.6.1	HEAD AND NECK CANCER Prevalence and attributes of head	389
303		and neck cancer	389
366	13.6.2	Dopamine and DARPP-32 in head and neck and esophageal cancers	389
366	13.6.3	Role of the cGMP/PDE/PKG pathway	507
366	101010	in head and neck cancer	390
367	13.7	NEUROLOGICAL AND	
368		NEUROENDOCRINE TUMORS	391
368	13.7.1	Dopamine in brain tumors: Glioblastoma	
368	1070	and meningioma	392
	13.7.2 13.7.3	Dopamine and neuroblastoma Prevalence and attributes of neuroendocrine	393
	13.7.3	tumors	394
	13.7.4	Dopamine in neuroendocrine tumors	395
373	13.8	SYNOPSIS	397
373	REFE	RENCES	397
373	NEI EI		571
272	Gloss	sarv	403
373 374	Index		403
5/4	mac		115