

**neuro**

# Neurotransmitters and other chemical signalling agents

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## Small-molecule neurotransmitters

## Acetylcholine (ACh)

### Precursors:

Choline and acetyl-CoA

### Synthesising enzymes:

Choline acetyl transferase

### Metabolising enzymes:

Acetylcholinesterase

### Metabolite:

Choline and acetate

Receptor subtypes	Agonists	Antagonists	Second messenger
M1 muscarinic	Methacholine	Pirenzepine, telenzepine	PI
M2	Methacholine	Himbacine, methoctramine	(-ve)cAMP, (+ve)gK+
M3	Methacholine	Hexahydrosila- difenidol	PI
M4 M5 MB	Methacholine	Tropicamide	(-ve)cAMP PI
Nicotinic (neuronal/ ganglion type)	Dimethylphenyl- piperazinium, nicotine	mecamylamine, hexamethonium (+)tubocurarine blocks channel)	(+ve)g(cation)
Nicotinic (muscle type)	Suxamethonium (also causes depolarisation block)	alpha-bungarotoxin, (+)tubocurarine (decamethonium blocks channel)	(+ve)g(cation)

## Adenosine (P<sub>1</sub> purinoceptors)

### Precursors:

Mainly AMP (from released ATP)

### Synthesising enzymes:

Mainly 5'-nucleotidase  
 Metabolising enzymes:  
 Adenosine deaminase  
 Metabolite:  
 Inosine

Receptor subtypes	Agonists	Antagonists	Second messenger
A <sub>1</sub>	CPA, R-PIA, GR 79236	8PT, DPCPX	(-ve)cAMP
A <sub>2A</sub>	CGS21680, CV-1808	8PT, CGS 15943	(+ve)cAMP
A <sub>2B</sub>	Metrifudil	8PT	(+ve)cAMP
A <sub>3</sub> MB	R-PIA, NECA	none	(-ve)cAMP

### ATP (P<sub>2</sub> purinoceptors)

Precursors:

Normal cellular constituent; formed from ADP

Synthesising enzymes:

Phosphorylases

Metabolising enzymes:

Phosphatases

Metabolites:

ADP, AMP, adenosine, inosine

Receptor subtypes	Agonists	Antagonists	Second messenger
P <sub>2X</sub>	beta-gamma-Me-ATP	alpha-beta-Me-ATP (desensitises) suramin	(+ve)g(cation) or (up)gCa <sup>2+</sup>
P <sub>2Y</sub>	ADP-beta-F, 2-Me-S-ATP	Reactive blue 2, suramin	PI, (+ve)gK
P <sub>2T</sub> (platelet)	ADP	Suramin, AMP	(-ve) cAMP, (+ve)g(cation)
P <sub>2Z</sub> (mast cell)	ATP <sup>4-</sup>	none	?
P <sub>2U</sub>	UTP	none	PI

## Monoamines (biogenic amines)

### Norepinephrine (Noradrenaline; NA) and Epinephrine (Adrenaline; AD)

#### Precursors:

L-Tyrosine (a) -> L-DOPA, (b) -> dopamine, (c) -> noradrenaline, (d) -> adrenaline

#### Synthesising enzymes:

(a) tyrosine hydroxylase, (b) L-aromatic amino-acid decarboxylase, (c) dopamine-beta-hydroxylase, (d) phenylethanolamine-N-methyl transferase

#### Metabolising enzymes:

MAO and COMT

#### Metabolites:

Vanillylmandelic acid (VMA) and 3-methoxy-4-hydroxyphenylglycol (MHPG)

Receptor subtypes	Agonists	Antagonists	Second messenger
alpha <sub>(1A)</sub>	Phenylephrine	Prazosin, (+)-niguldipine	PI
alpha <sub>(1B)</sub>	Phenylephrine	Prazosin, CEC	PI
alpha <sub>(1C)</sub>	Phenylephrine	Prazosin, CEC	PI
alpha <sub>(2A)</sub>	Oxymetazoline	Yohimbine, fluparoxan	(-ve)cAMP, (down)gCa <sup>(2+)</sup> , (down)gK <sup>+</sup>
alpha <sub>(2B)</sub>	UK14304	Prazosin, ARC 239	(-ve)cAMP, (down)gCa <sup>(2+)</sup>
alpha <sub>(2C)</sub>	UK14304	Yohimbine	(-ve)cAMP
beta <sub>(1)</sub>	Xamoterol, RD363	Practolol, atenolol, CGP20712A	(+ve)cAMP
beta <sub>(2)</sub>	Salbutamol, salmeterol, procaterol	ICI 118551	(+ve)cAMP
beta <sub>(3)</sub>	BRL 37344 BRL 35135	cyanopindolol	(+ve)cAMP

## Dopamine (DA)

### Precursors:

Tyrosine (a) → L-dihydroxyphenylalanine (L-DOPA), (b) -7gt; dopamine

### Synthesising enzymes:

(a) Tyrosine hydroxylase; (b) L-aromatic amino-acid decarboxylase (DOPA decarboxylase)

### Metabolising enzymes:

MAO and catechol-O-methyl transferase (COMT)

Metabolite:

3,4-Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)

Receptor subtypes	Agonists	Antagonists	Second messenger
D <sub>1</sub>	SKF 38393	Sch 23390	(+ve) cAMP
D <sub>2</sub>	Quinpirole	Sulpiride	(+ve)gK+
D <sub>3</sub>	7-OH-DPAT	AJ-76	?
D <sub>4</sub>	Dopamine	Clozapine	?
D <sub>5</sub>	Dopamine	Sch 23390	(+ve)cAMP

### 5-Hydroxytryptamine (5-HT; serotonin)

Precursors:

Tryptophan (a) -> 5-hydroxytryptophan (b) -> 5HT

Synthesising enzymes:

(a) Tryptophan hydroxylase, (b) 5HTP decarboxylase

Metabolising enzymes:

Monoamine oxidase (MAO)

Metabolite:

5HIAA

Receptor subtypes	Agonists	Antagonists	Second messenger
5HT <sub>(1A)</sub>	8-OH-DPAT	Way 100135, SDZ 216-525	(-ve) cAMP
5HT <sub>(1B)</sub>	CP 93129	Cyanopindolol	(-ve) cAMP
5HT <sub>(1C)</sub>	now re-classified as 5HT <sub>(2C)</sub>		
5HT <sub>(1D)</sub>	5CT, sumatriptan	Methiothepin, methysergide	(-ve) cAMP
5HT <sub>(1D-alpha)</sub> MB			
5HT <sub>(1DB)</sub> MB (human homologue of the rodent 5HT <sub>1B</sub> receptor)			
5HT <sub>(1E-alpha)</sub> MB			(-ve) cAMP
5HT <sub>(1EB)</sub> MB			(-ve) cAMP
5HT <sub>(1F)</sub> MB			(-ve) cAMP
5HT <sub>(2A)</sub> (old 5HT <sub>(2)</sub> )	DOI	Ketanserin	PI
5HT <sub>(2B)</sub> (rat fundus)	DOI	Ketanserin	PI
5HT <sub>(2C)</sub> (old 5HT <sub>1C</sub> )	mCPP	Mesulergine	PI
5HT <sub>(3)</sub>	2-Me-5HT	Ondansetron, granisetron	(+ve)g(cation)
5HT <sub>(4)</sub>	5MeOTrp, cisapride	GR 113808	(+ve)cAMP
5HT <sub>(5)</sub> MB	<i>(binds bufotenine)</i>		

## Histamine (HA)

Precursors:

Histidine

Synthesising enzymes:

Histidine decarboxylase

Metabolising enzymes:

Histamine-N-methyl transferase, histaminase, etc.

Metabolite:

Methylhistamine, IAA and others

Receptor subtypes	Agonists	Antagonists	Second messenger
H <sub>(1)</sub>	2-thiazolyl-ethylamine	Mepyramine	PI
H <sub>(2)</sub>	Dimaprit	Ranitidine, cimetidine	(+ve)cAMP
H <sub>(3)</sub>	(R)-alpha-methyl histamine	Thioperamide	?

## Excitatory amino acids (EAA)

### Glutamate (Glu) (and Aspartate)

Precursors:

None

Synthesising enzymes:

None

Metabolising enzymes:

Glutamate transaminase (uptake is more important)

Metabolite:

Glutamine



Receptor subtypes	Agonists	Antagonists	Second messenger
NMDA (subtypes <b>MB</b> )	NMDA, AP5, CPP	CGP37849 (MK801 is a channel blocker, PCP is non-competitive)	(+ve)g(cation)
AMPA (subtypes <b>MB</b> )	AMPA, quisqualate	NBQX, NQX DNQX	(+ve)g(cation)
Kainate (subtypes <b>MB</b> )	Kainate, domoate	NBQX, NQX DNQX	(+ve)g(cation)
Metabotropic (subtypes <b>MB</b> )	1S,3R-ACPD, ibotenate	None	PI

## Inhibitory amino acids (IAA)

### gamma-Aminobutyric Acid (GABA)

Precursors:

Glutamate

Synthesising enzymes:

Glutamic acid decarboxylase (GAD)

Metabolising enzymes:

GABA transaminase

Metabolite:

Succinic semialdehyde

Receptor subtypes	Agonists	Antagonists	Second messenger
GABA <sub>A</sub>	Muscimol, THIP, isoguvacin	Bicuculline, picrotoxin	(+ve)gCl
GABA <sub>B</sub>	Baclofen, CGP 97541	2-OH-Saclofen, CGP 35348	(-ve)gK+, (-ve)gCa2+, (-ve)cAMP
Benzodiazepine site on GABAA receptor	Diazepam (DMCM is an inverse agonist)	Flumazenil	Enhances (+ve)gCl- by GABA

## Glycine (Gly)

Precursors:

None

Synthesising enzymes:

None

Metabolising enzymes:

None (uptake is more important)

Metabolite:

None

Receptor subtypes	Agonists	Antagonists	Second messenger
Glycine	Glycine	Strychnine	(+ve)gCl-
Allosteric site on NMDA receptor	Glycine	7-chloro-kynurenate	n/a

## Large-molecule neurotransmitters (neuropeptides) and other substances

### Angiotensin II (AT II)

Precursors:

Angiotensin I

Synthesising enzymes:

Angiotensin converting enzyme (ACE)

Metabolising enzymes:

Aminopeptidase

Metabolite:

Angiotensin III

Receptor subtypes	Agonists	Antagonists	Second messenger
AT <sub>1</sub>	Angiotensin II,III	Losartan (DuP753), GR 117289	PI, (-ve)cAMP
AT <sub>2</sub>	Angiotensin II,III	PD 123177, PD 123319, CGP42112	(-ve)cGMP

## Bradykinin (BK)

Precursors:

Kininogens

Synthesising enzyme:

Kallikrein

Metabolising enzyme:

ACE, kininase I (carboxypeptidase-N)

Metabolites:

Des-Arg<sup>9</sup>-bradykinin, other fragments

Receptor subtypes	Agonists	Antagonists	Second messenger
B <sub>1</sub>	Des-Arg <sup>9</sup> -BK	Des-Arg <sup>9</sup> , Leu <sup>8</sup> -BK Des-Arg <sup>10</sup> -HOE140	?
B <sub>2</sub>	Hyp <sup>9</sup> ,Tyr(Me) <sup>8</sup> -BK	NPC567, HOE140, NPC349	PI

## Cholecystokinin (CCK) (and Gastrin (G))

### Precursors:

Preprocholecystokinin

### Synthesising enzymes:

Post-translational peptidases

### Metabolising enzymes:

Endopeptidase EC 24:11

### Metabolite:

Peptide fragments

Receptor subtypes	Agonists	Antagonists	Second messenger
CCK <sub>(A)</sub>	A71378	Devazepide, lorglumide	PI
CCK <sub>(B)</sub>	CCK4	L365260, PD134308	?
Gastrin *	G17	L365260	PI

\* may be identical to CCK<sub>(B)</sub>

## Enkephalin (met- and leu-) and Dynorphin

### Precursors:

Proenkephalin and prodynorphin

### Synthesising enzymes:

Peptidases

### Metabolising enzymes:

Enkephalinase (EC 24:11) and other peptidases

### Metabolite:

Peptide fragments

Receptor subtypes	Agonists	Antagonists	Second messenger
$\mu$ -opoid	DAGOL (DAMGO)	Naloxone	(-ve)cAMP, (+ve)gK <sup>+</sup>
delta-opoid	DPDPE	Naltrindol	(-ve)cAMP, (+ve)gK <sup>+</sup>
kappa-opoid	U69593, CI 977, dynorphin	Norbinaltorphimine	(-ve)gCa <sup>2+</sup>

### Endothelin (ET)

Precursors:

preproET-1 etc.

Synthesising enzymes:

"endothelin converting enzyme"

Metabolising enzymes:

not known

Receptor subtypes	Agonists	Antagonists	Second messenger
ET <sub>(A)</sub>	ET-1, ET-2	FR139317, BQ123	PI
ET <sub>(B)</sub>	Sarafotoxin S6C, [Ala <sup>(1),(3),(11),(15)</sup> ] ET-1, BQ 3020	IRL 1038	PI
ET <sub>(C)</sub> MB			

### Nitric Oxide (NO; formerly EDRF)

Precursors:

L-arginine

**Synthesising enzymes:**

NO synthase

**Metabolising enzymes:**

none: diffusion and spontaneous breakdown

**Metabolite:** $\text{NO}_{(2)}^-$ ,  $\text{NO}_{(3)}^-$ 

NO has no conventional receptor, but it activates guanylate cyclase directly. It can be generated by glyceryl trinitrate or sodium nitroprusside. The synthetic enzyme can be inhibited by L-NMMA and L-NAME. Three NO synthases have been cloned, of which one (in macrophages) is inducible, and two (in brain and endothelium) are constitutive.

**Prostanoids (Prostaglandins, prostacyclin and thromboxane)****Precursors:**

arachidonic acid (i.e. eicosatetraenoic acid; 2-series prostanoids), eicosatri- and eicosapentaenoic acids

**Synthesising enzymes:**Prostaglandin synthetase (cyclooxygenase), PGI<sub>2</sub> synthase, TX synthase.**Metabolising enzymes:**

15-hydroxyprostaglandin dehydrogenase, PG-9-keto-reductase

**Metabolites:**

large number of oxidised metabolites

Receptor subtypes (most potent natural prostanoid)	Agonists	Antagonists	Second messenger
DP (PGD <sub>(2)</sub> )	BW245C, ZK110841	BWA868C, AH6809	<87>cAMP
EP (PGE <sub>(2)</sub> ), subdivided as shown:			
EP <sub>(1)</sub>	sulprostone, iloprost	AH6809, SC-19220	PI
EP <sub>(2)</sub>	AY23626, butaprost, rioprostil	none	<87>cAMP
EP <sub>(3)</sub>	sulprostone AY23626, rioprostil, enprostil, GR 63799	none	PI, <51>cAMP
FP (PGF <sub>(2-alpha)</sub> )	fluprostenol, cloprostenol	none	PI
IP (PGI <sub>(2)</sub> )	iloprost,cicaprost	none	<87>cAMP
TP (TXA <sub>(2)</sub> )	U-46619, STA2, EP171	GR32191, EP092, BM13505, SQ28668	PI

### Substance P (SP) and Neurokinins A and B (NKA, NKB)

Precursors:

Preprotachykinins

Synthesising enzymes:

Peptidases

Metabolising enzymes:

ACh-esterase, EC 24.11

Metabolite:

Peptide fragments

Receptor subtypes	Agonists	Antagonists	Second messenger
NK <sub>(1)</sub>	SPOMe, GR 73632, Sar <sup>9</sup> Met(O <sub>2</sub> ) <sup>11</sup> SP	GR82334, RP67580, CP-99994	PI
NK <sub>(2)</sub>	GR 64349	L-659877, SR48968, MEN10207, GR94800, GR100679	PI
NK <sub>(3)</sub>	Senktide	GR138676	PI

### Other neurotransmitter substances



Neurotransmitter	Abbreviation
Antidiuretic hormone (vasopressin)	ADH
Atrial natriuretic peptide	ANP or ANF
Bombesin	
Calcitonin-gene-related peptide	CGRP
Corticotrophin-releasing factor	CRF
Galanin	--
Leukotriene	LT
Luteinising hormone releasing hormone	LHRH
Melatonin	--
Neuropeptide Y	NPY
Neurotensin	NT
Oxytocin	--
Pancreatic polypeptide (human)	(h)PP
Peptide YY	PYY
Platelet aggregating factor	PAF
Somatostatin	SS or SRIF
Taurine	--
Thyrotropin-releasing hormone	TRH
Vasoactive intestinal polypeptide	VIP

**NB:** (+ve) indicates increase; (-ve) indicates decrease.

