

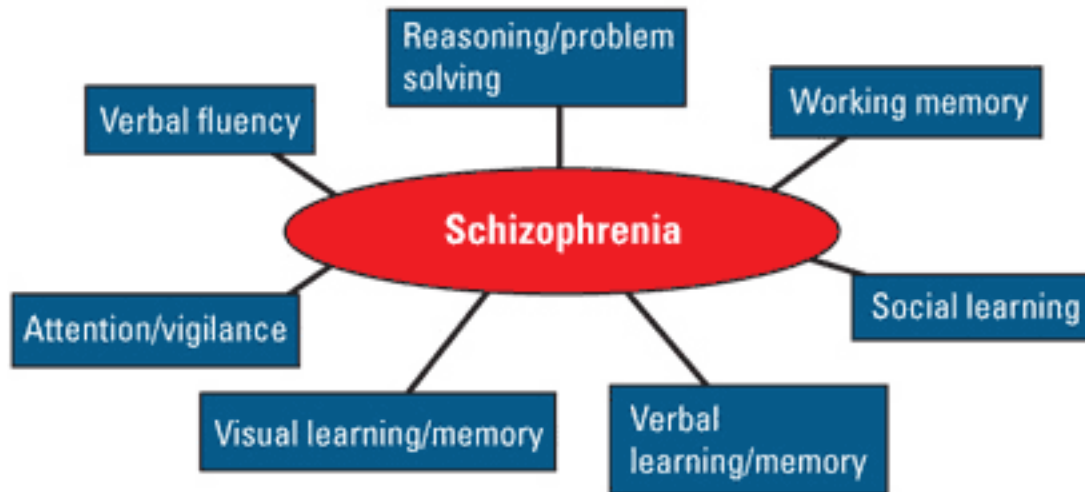
5. Het nicotine systeem, basics

Richard

- Nicotine, Muscarine receptoren,
 - perifeer,
 - centraal,
- Wat voor soort receptoren zijn dit?
 - (langzaam? Snel? Ion-kanaal)
- geneesmiddelen die hier op inwerken.

MATRICES

Neuropsychological deficits in schizophrenia.¹⁶



The MATRICS group determined seven separable cognitive dimensions that are affected in schizophrenia.

MATRICES=Measurement and Treatment Research to Improve Cognition in Schizophrenia.

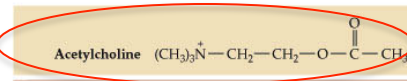
Acetylcholine:

- Motoriek**
- Aandacht**
- Leren**
- Geheugen**

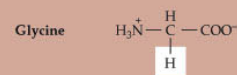
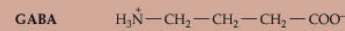
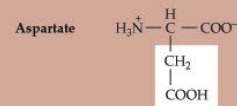
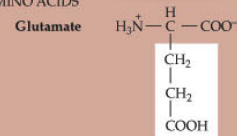
Target in Alzheimer en Parkinsonen
myasthenia gravis

Acetylcholine:

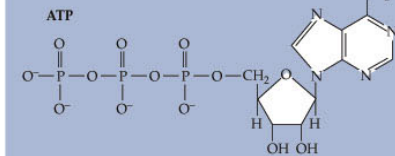
SMALL-MOLECULE NEUROTRANSMITTERS



AMINO ACIDS

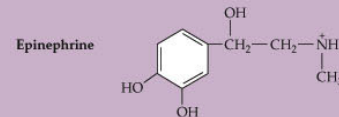
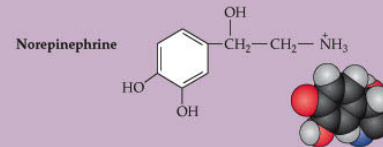
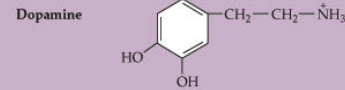


PURINES

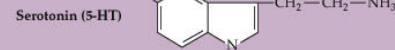


BIOGENIC AMINES

CATECHOLAMINES



INDOLEAMINE

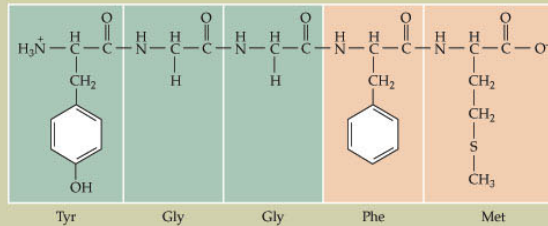
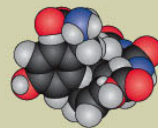


IMIDAZOLEAMINE



PEPTIDE NEUROTRANSMITTERS (more than 100 peptides, usually 3-30 amino acids long)

Example: Methionine enkephalin (Tyr-Gly-Gly-Phe-Met)



Acetylcholine

Muscarine Receptor



Nicotine Receptor



snel: ion kanaal receptoren
(ionotropic)
snel

neuromodulatie: G-protein gekoppelde receptoren
(metabotropic)
langzaam

(C)

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α_{1-7}	$\alpha 1$	α_{2-9}	5-HT ₃	P _{2X1}
	Glu R2	NR2A	Glu R6	β_{1-4}	$\alpha 2$	β_{1-4}		P _{2X2}
	Glu R3	NR2B	Glu R7	γ_{1-4}	$\alpha 3$	γ		P _{2X3}
	Glu R4	NR2C	KA1	δ	$\alpha 4$	δ		P _{2X4}
		NR2D	KA2	ϵ	β			P _{2X5}
			ρ_{1-3}					P _{2X6}
								P _{2X7}

(B)

Receptor class	Glutamate	GABA _B	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	GABA _B R1	D1 _A	$\alpha 1$	H1	5-HT 1	A type	M1
	mGlu R1	GABA _B R2	D1 _B	$\alpha 2$	H2	5-HT 2	A1	M2
	mGlu R5		D2	$\beta 1$	H3	5-HT 3	A2a	M3
	Class II		D3	$\beta 2$		5-HT 4	A2b	M4
	mGlu R2		D4	$\beta 3$		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P _{2X}	
	mGlu R4						P _{2Y}	
mGlu R6						P _{2Z}		
mGlu R7						P _{2T}		
mGlu R8						P _{2U}		

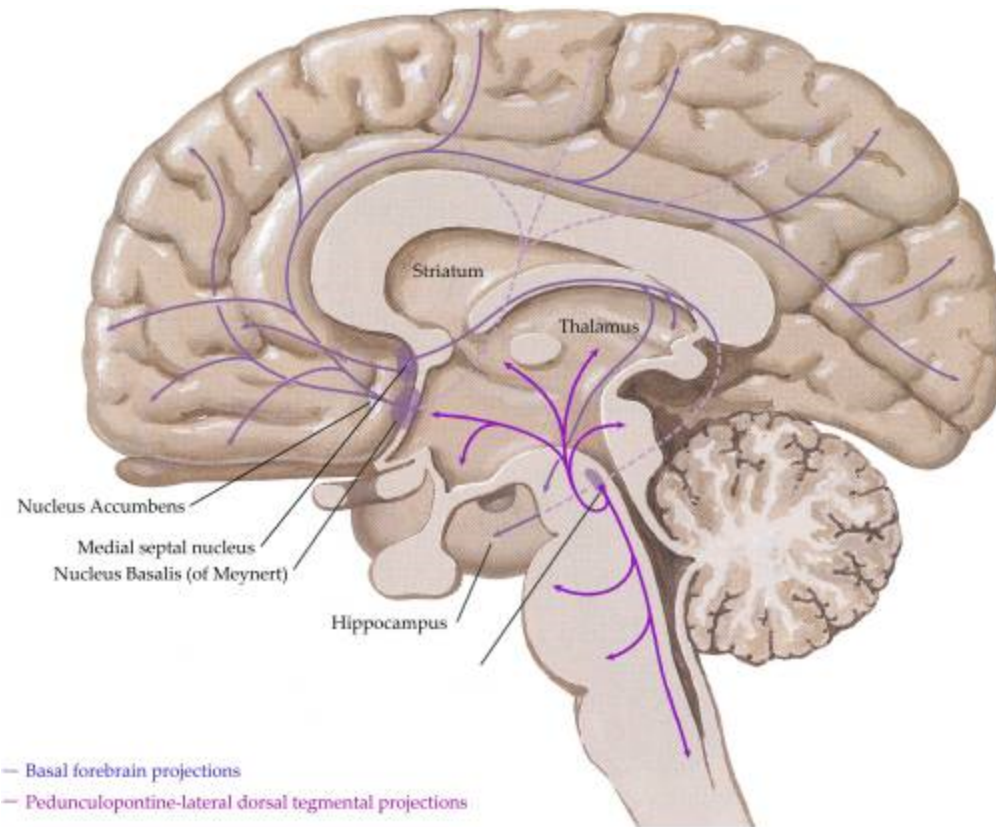
**Spier
Neuronaal**

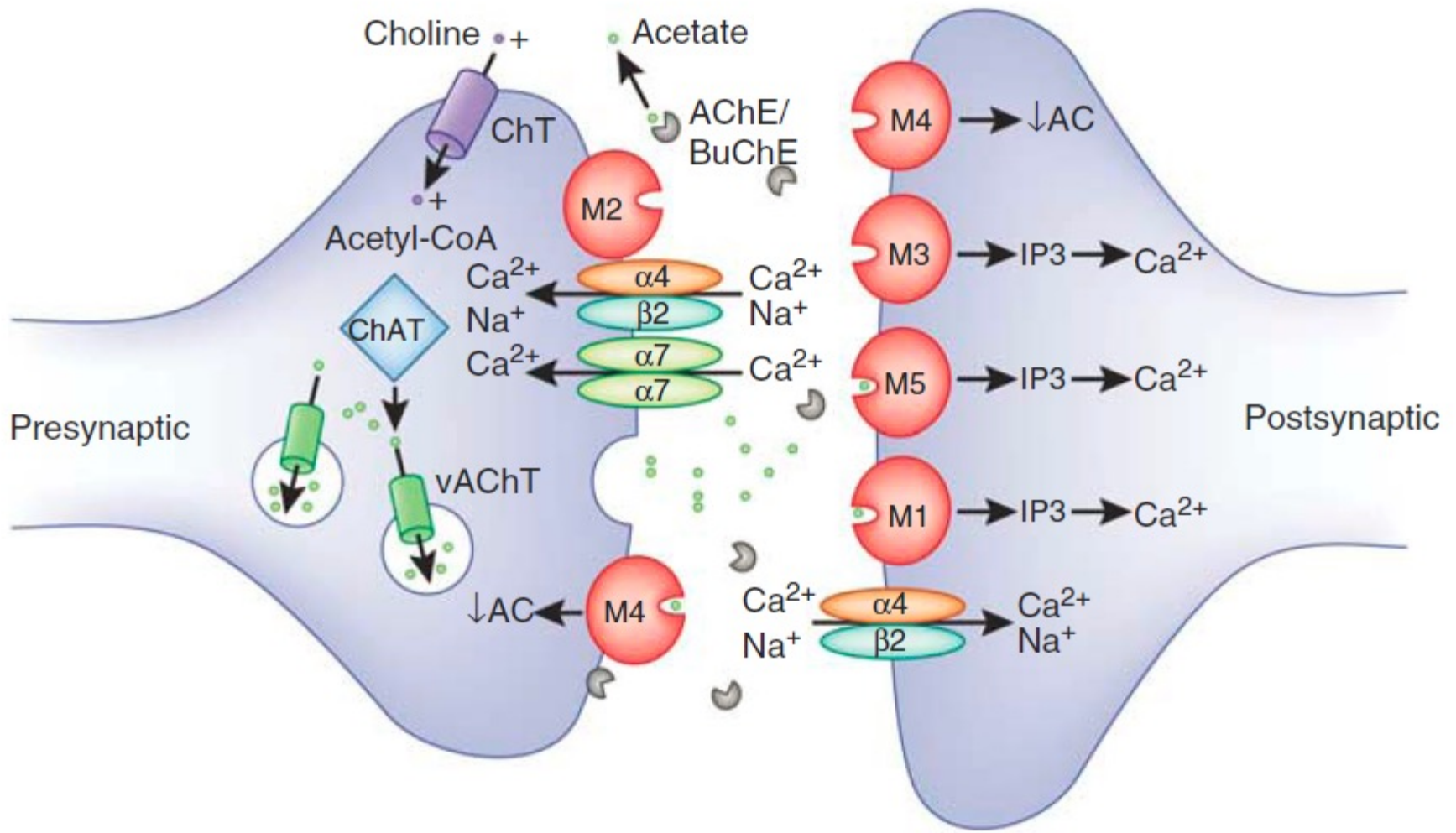
Nicotine Receptor

**Rest & digest
Neuronaal**

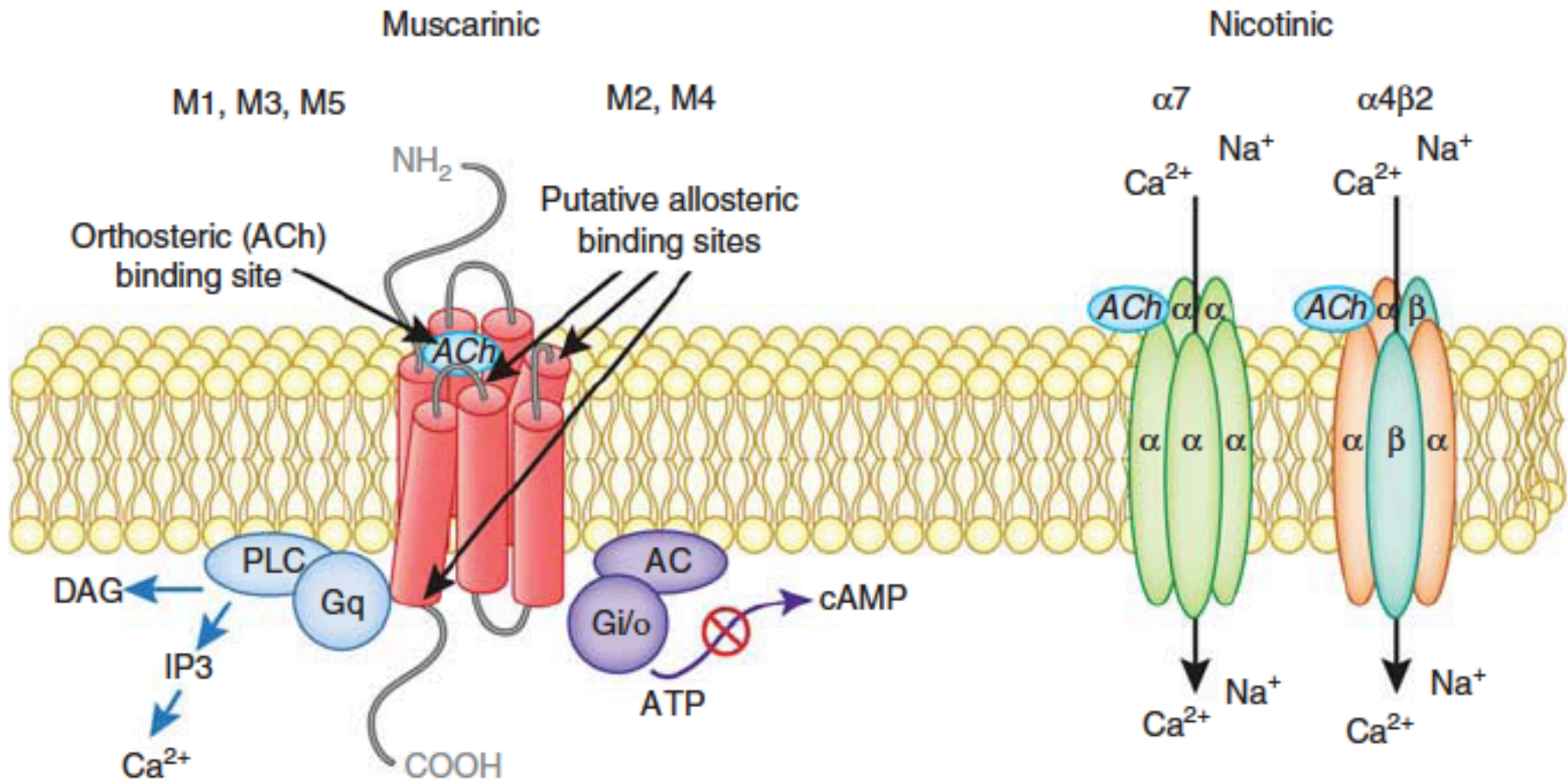
Muscarine Receptor

- Projecties: - vanuit hersenstam
- vanuit basale kernen Meynert
- interneuronen in striatum





Problemen vinden specifieke compounds...



- Key effectors (examples)**
- ↑ PLCβ
 - ↑ [Ca²⁺]_i
 - ↑ MAPK

- Key effectors (examples)**
- ↑ AC
 - ↑ MAPK
 - ↑ GIRK ch.

- Key effectors (examples)**
- ↑ [Ca²⁺]_i
 - ↑ VDCC
 - ↑ PKC



Cholinerge hypothese psychose (1975)

Postmortem studies:

- verlaagde muscarine en nicotine receptoren in patienten met SCZ
- verlaagde ChAT in patienten met SCZ

Challenge studies:

- mACh en nACh receptor antagonist verergeren positieve/cognitieve symptomen in patienten met SCZ en induceren deze in gezonde vrijwilligers
- mACh en nACh agonist en AChEI kunnen symptoomverlichting geven

TABLE 2.**Location and Function of Muscarinic Receptors^{18-21,23,24,35-44}**

	<i>Location</i>	<i>Cellular Function</i>	<i>Systemic Function</i>	<i>Changes in Schizophrenia</i>
M ₁	Striatum, cortex, hippocampus	Gq; Postsynaptic, modulate fast transmission and metabolic function	Learning, memory, possible role in some types of epilepsy, cleave amyloid precursor protein, IL-2 production	Down in hippocampus, striatum, PFC, NAc
M ₂	Basal forebrain, thalamus, heart, brainstem, pupil, exocrine glands, spinal cord	Gi; Presynaptic inhibitory auto/heteroreceptor	Salivation, akinesia, bradycardia, smooth muscle contractility, bronchoconstriction, tremor, hypothermia, analgesia, axonal growth	Down in striatum
M ₃	Brain (evenly distributed), pupil, hypothalamus, exocrine glands, peripheral arteries	Like M ₁	Salivation, smooth muscle contractility, vasorelaxation, NO release, appetite	Unknown
M ₄	Striatum, cortex, hippocampus, spinal cord	Like M ₂ plus inhibitory postsynaptic	Regulate striatal DA release, modulate PPI, analgesia, keratinocyte migration	Down in hippocampus, striatum, PFC, NAc
M ₅	DA neurons, basal ganglia, brain vasculature	Like M ₁	Cerebral arterial vasorelaxation	Unknown

M=muscarinic; Gq=G protein that activates phospholipase C; Gi=inhibitory G protein; PFC=prefrontal cortex; DA=dopaminergic; NAc=nucleus accumbens; PPI=pre-pulse inhibition.