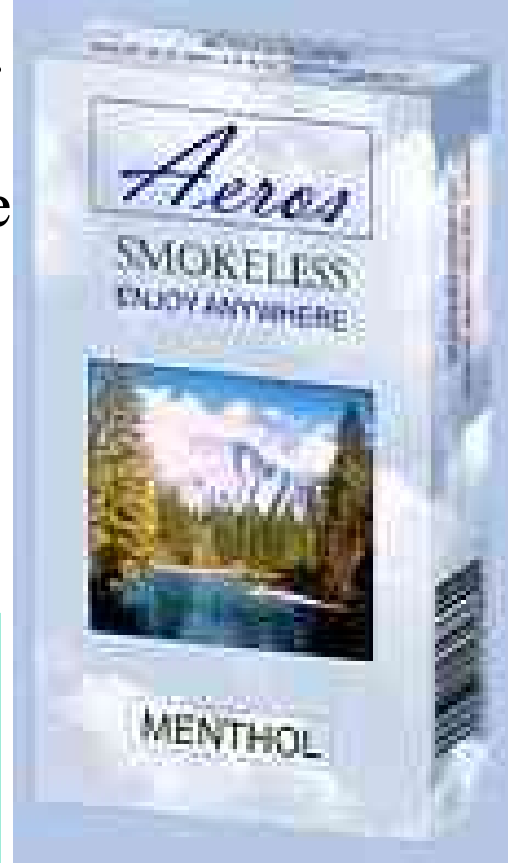


"Using a **Ruyan**, you can **keep your smoking habits**,.. **enjoy** the same pleasure as that of traditional cigarette when inhaling the nicotine smog droplet, imitating the whole process of smoking. RUYAN Cigarette creates a **healthy smoking cultural atmosphere**, and has been eulogized by authoritative experts as the perfect combination of modern micro-electronic technology, biological technology and the conception of **healthy life**".



advantage:
no products of pyrolysis
no passive smoking

undermine:
control of smoking bans,
denormalization,
deconditioning,
cessation.

promote:
multiple dependence
nicotine trade



Nicotine addiction

ICD-10: 17.2

Largest epidemic:

victims / year: 5½ millions

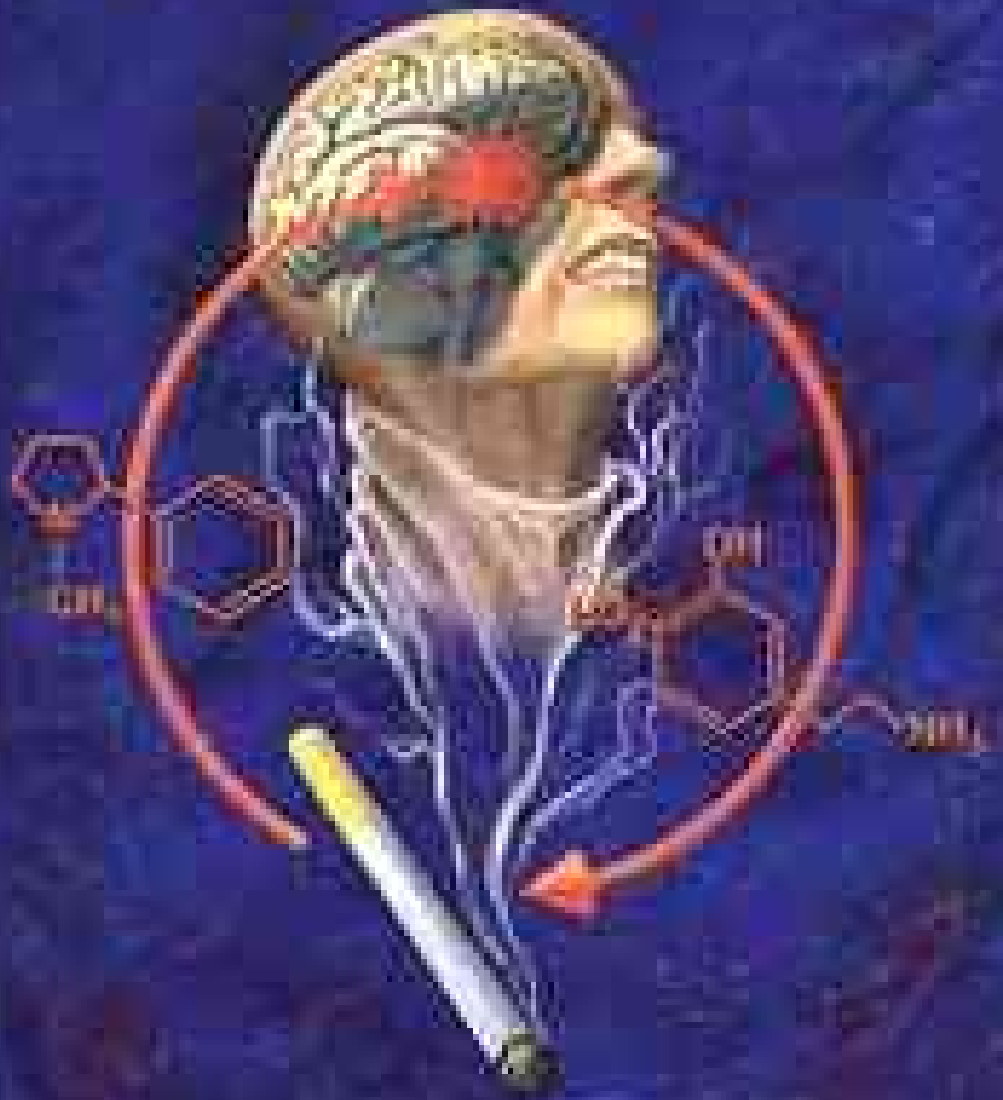
2030 approx. 8½ millions

Europe (2005) >½ million

Austria: smokers ~10 000

Austria: ETS ~ 1 000

NRT: harm reduction ?
or diversification, spread
and promotion of nicotine
products on the free market,
prolongation of addiction,
gateway drug for children?

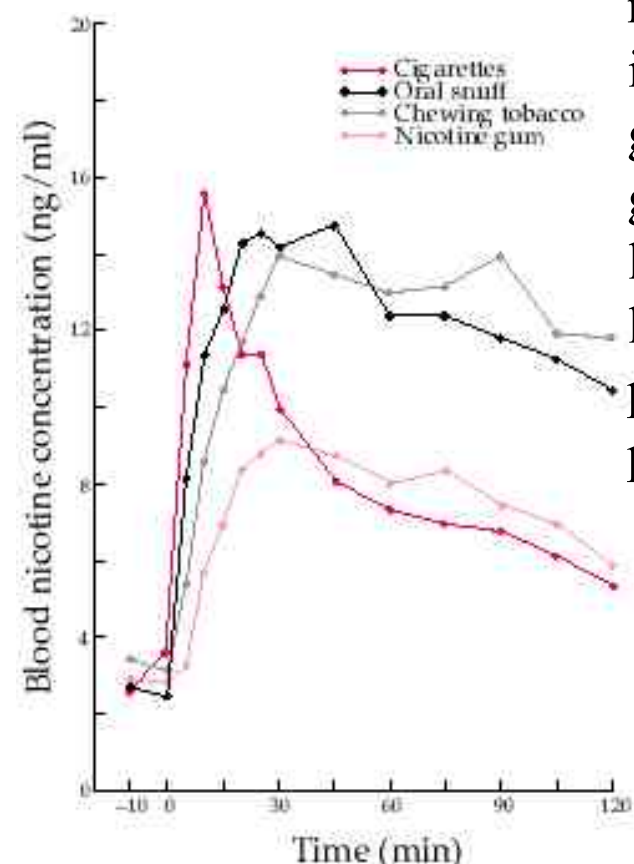


Nicotine in cigarette smoke (pH 5.8-6.2) 99% on fine particles, large surface and buffer (pH 7.4) enable rapid uptake of non-ionized, lipophilic nicotine (arterial concentration 2-3fold (up to 10fold) higher).

application	C_{max} (ng/ml)	T_{max} (min)	bioavail. %
	art (ven)	art (ven)	
1st cigarette (2mg), 5min	20-60 (15-30)	3-5 (5-8)	80-90
nasal spray (1mg)	10-15 (5-8)	4-6 (11-18)	60-80
inhaler (4mg), 20min	8 (30)	(30)	51-56
gum (4mg), 20min	10-17 (30)	(30)	55
gum (2mg), 20min	6-9 (30)	(30)	78
lozenge (4mg), 20-30min	10.8 (66)	(66)	79
lozenge (2mg), 20-30min	4.4 (60)	(60)	50
patch (21mg), 24h	18-23 (3-7h)	(3-7h)	68
patch (14mg), 24h	11-16 (4-7h)	(4-7h)	68

Hukkanen et al.: Pharmacol Rev 2005; 57: 79-115

patch: poor substitute
 low risk of addiction

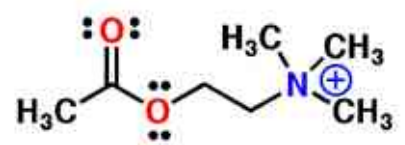


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 Neuropharmacology
 Fig. 14-1

nAChRs in the **autonomic & central** nervous systems and the neuromuscular junctions are found in part of five polypeptide subunits: many NACHR subtypes made of different subunit combinations: α 2-10, β 2-4,...

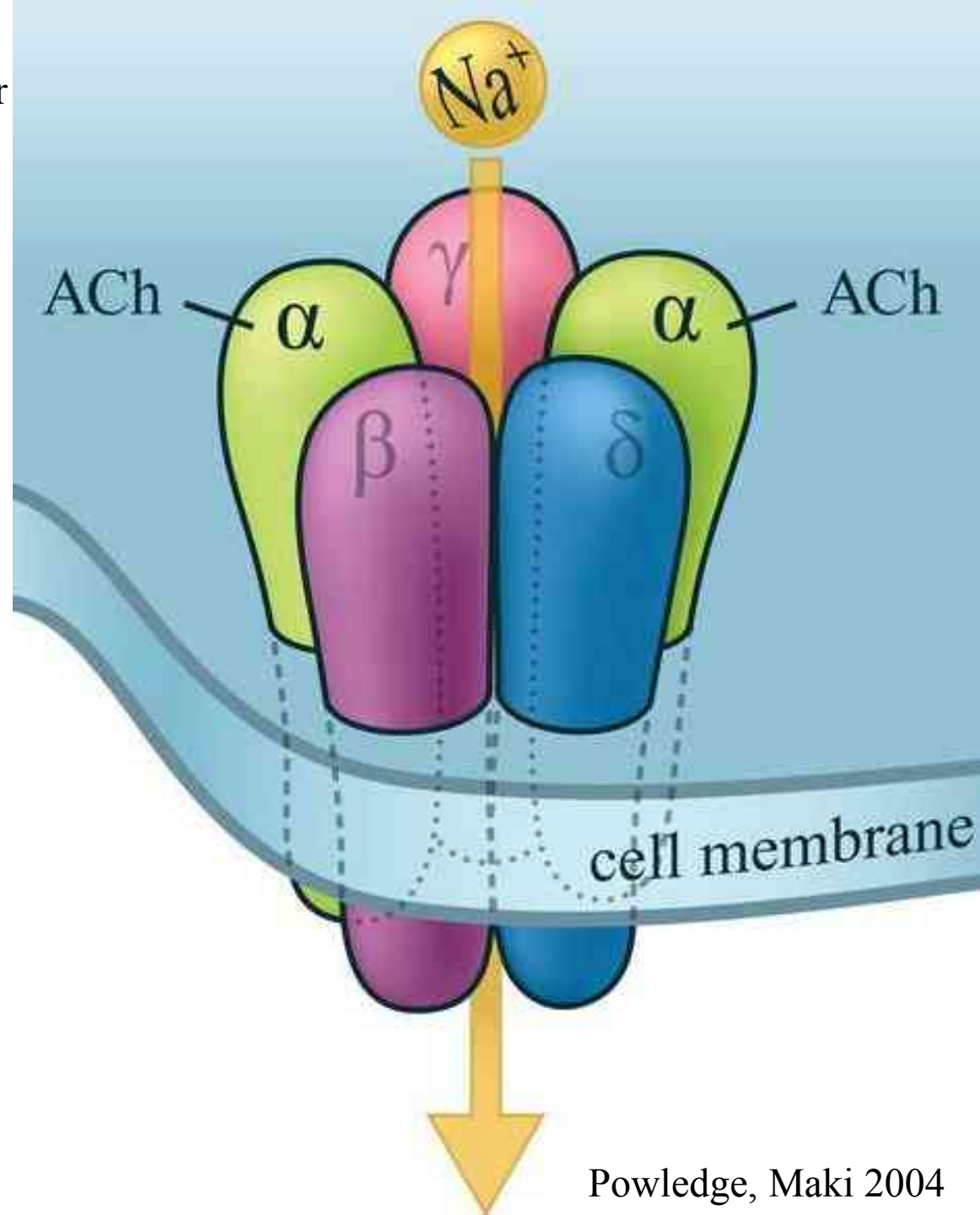
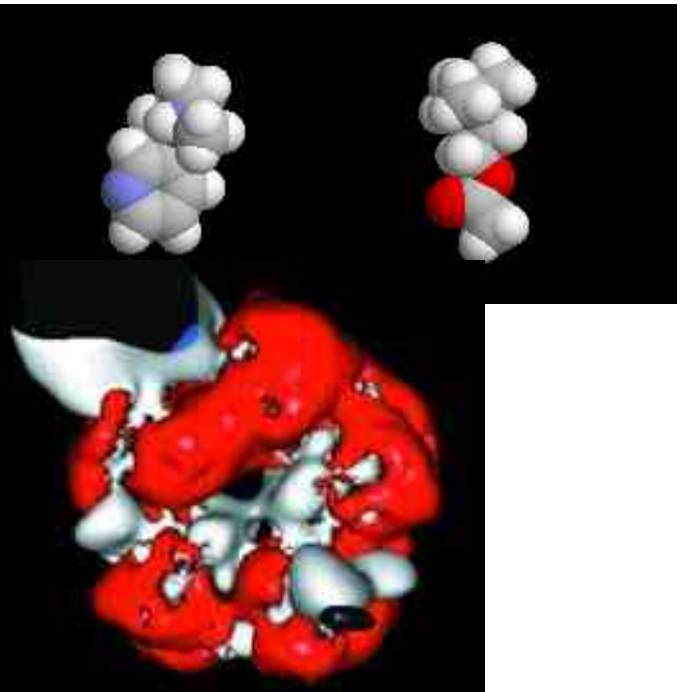


Nicotine



Acetyl Choline

similar charge distribution

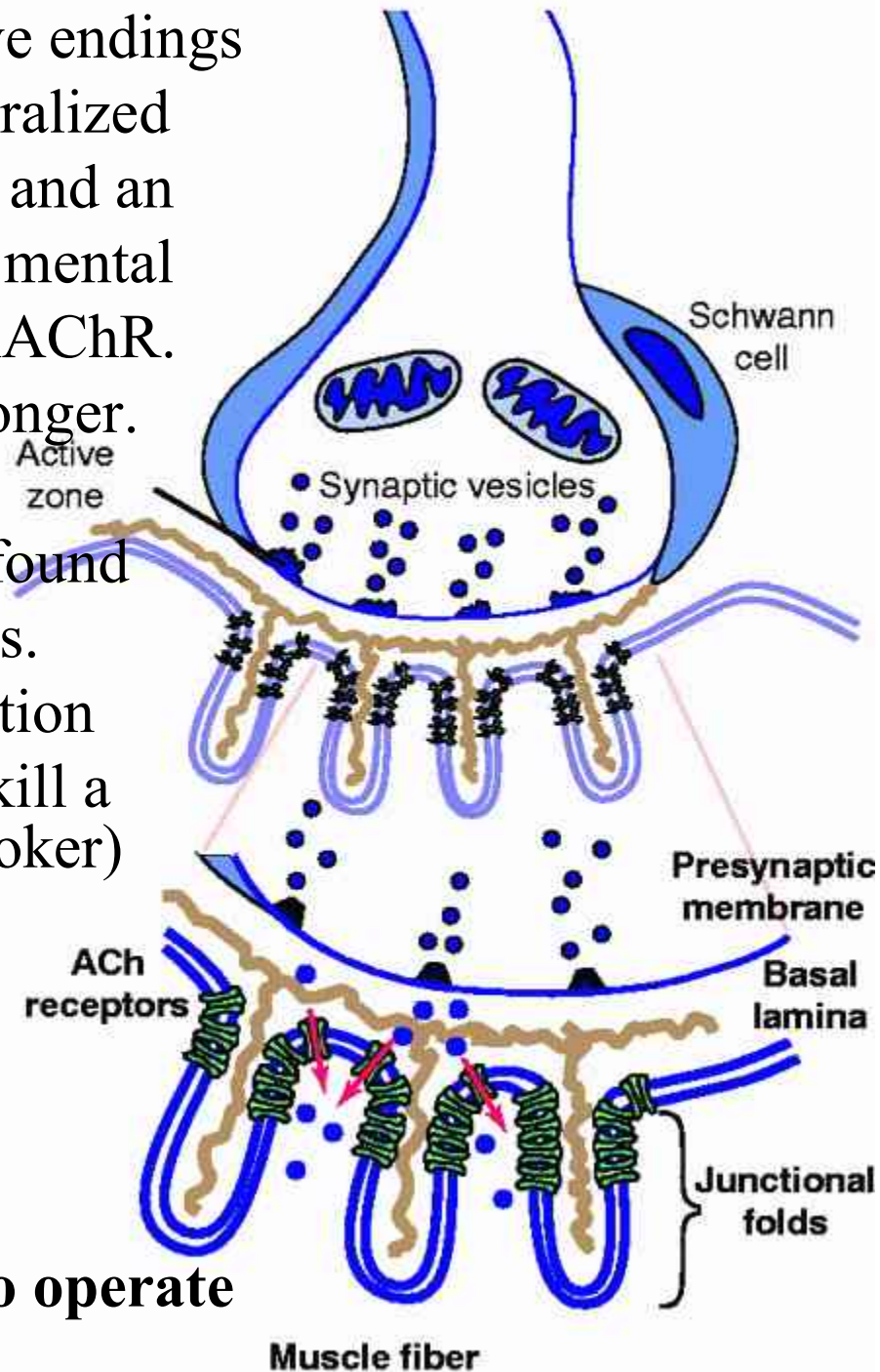
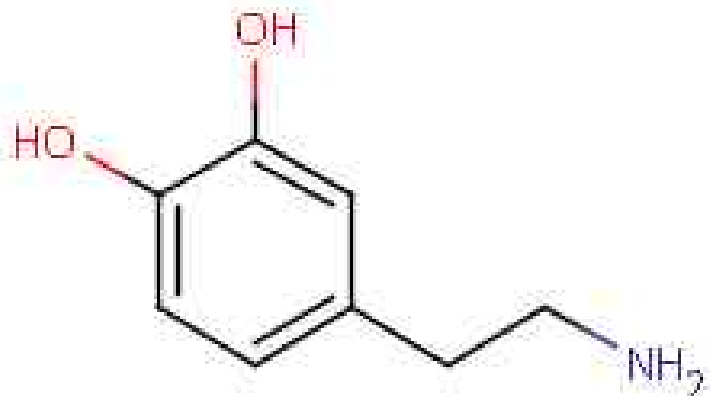


Nicotine stimulates vagal sensory nerve endings in the lungs, producing reflexly a generalized **relaxation** of the skeletal musculature and an **activation** of the EEG correlated with mental alertness. Sensory reward faster than nAChR. Block of receptor (higher dose) lasts longer.

Increase of receptors (+ sensitivity)

Upregulation in days up to weeks, found to persist one year in heavy smokers.

Tolerance is a result of overstimulation (nicotine of 40 cigarettes/day may kill a nonsmoker)



Nicotine resets the nervous system to operate at normal levels only in its presence.

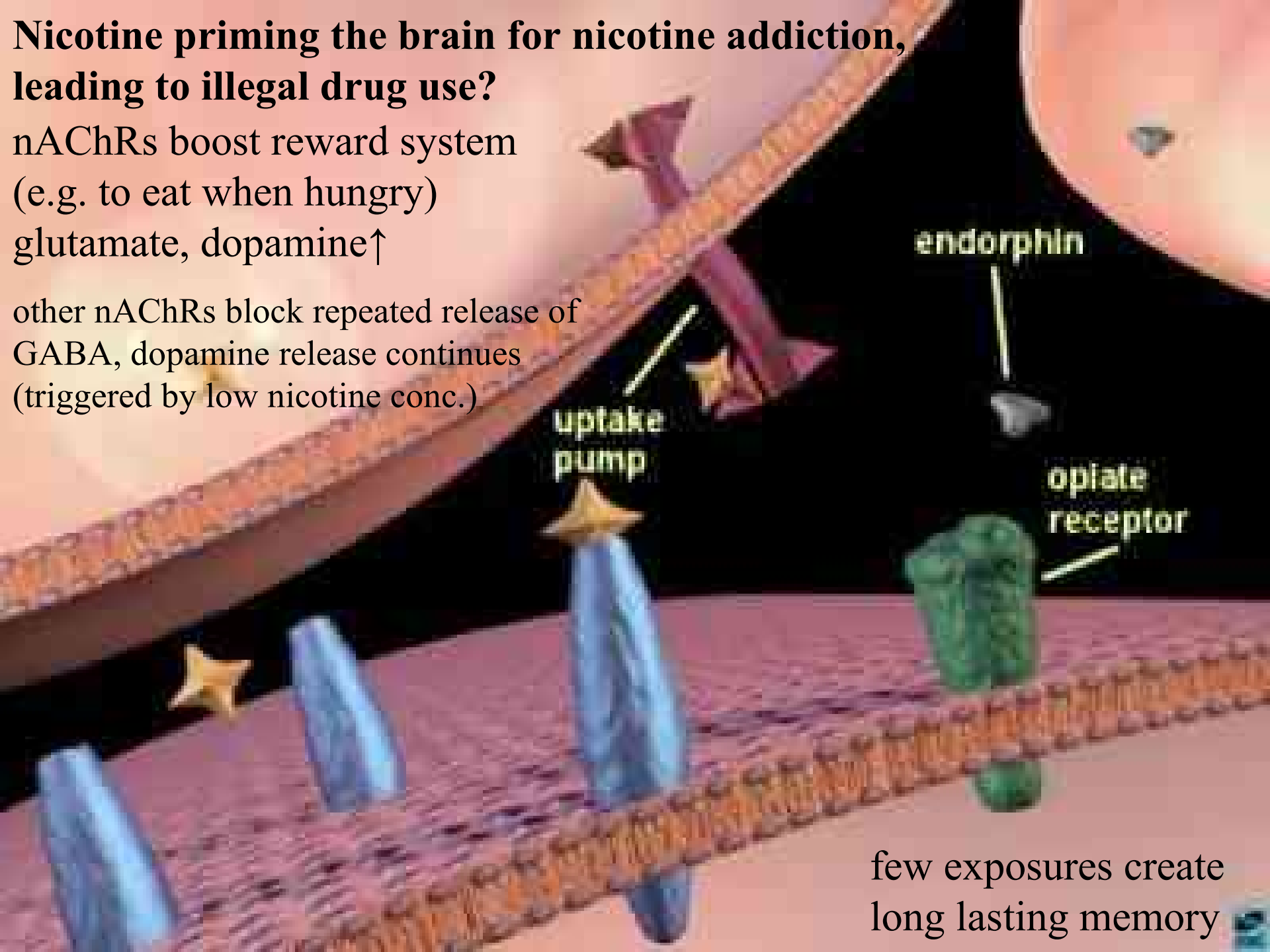
Nicotine priming the brain for nicotine addiction, leading to illegal drug use?

nAChRs boost reward system

(e.g. to eat when hungry)

glutamate, dopamine ↑

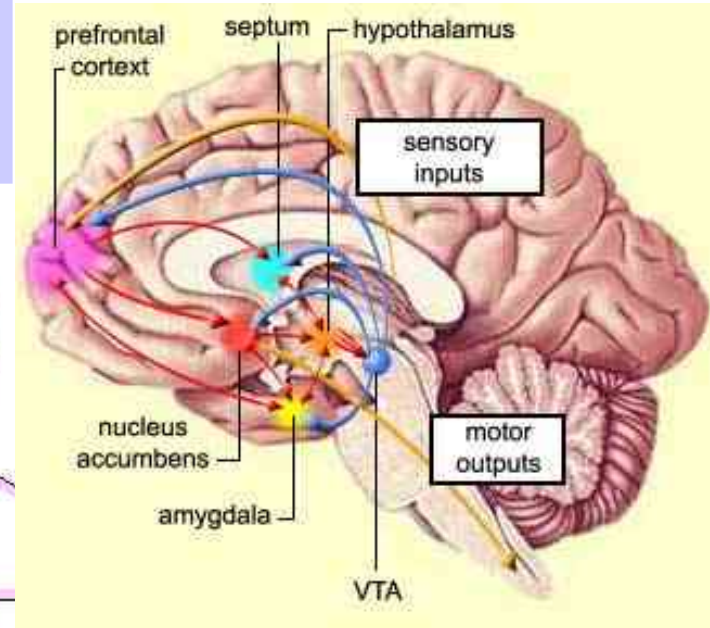
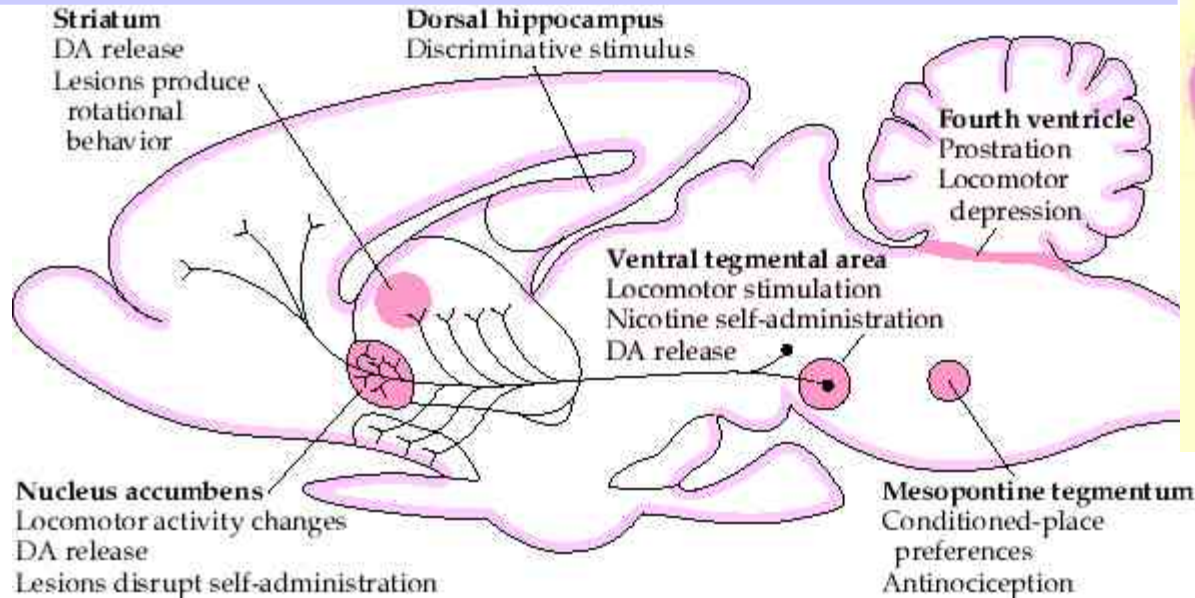
other nAChRs block repeated release of
GABA, dopamine release continues
(triggered by low nicotine conc.)



few exposures create
long lasting memory

nicotine releases several neurotransmitters/-modulators:
 dopamine (reward), noradrenaline (attention),
 acetylcholine (attention, perception), vasopressine (memory),
 serotonin (mood), beta-endorphine (anxiety, stress, pain↓),...

pain: reduced need of morphine (surgery), but
 increased mortality of intensive care patients
 given nicotine patch !



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 Pg. 11-01

Nicotine concentrations in **fetal** rat brain are
 2.5 times higher than the mother's blood nicotine

Many nicotine sellers recommend „reduced smoking“ (harm reduction).
ASH (UK) Dec.2005: NRT guidance for health professionals: **NRT can now be used while still smoking**,...(no conflicts of interests declared, despite pharma industry shares, consultancies, etc.)

Raw, McNeill, West, Arnott, Armstrong et al.

1-4 cigarettes per day triple the risk of dying from IHD and lung cancer

Bjartveit & Tverdal BMJ 2005

RR	females	males
IHD	2.94 (1.75 to 4.95)	2.74 (2.07 to 3.61)
lung cancer	5.03 (1.81 to 13.98)	2.79 (0.94 to 8.28)

nicotine promotes cancer: NNK: growth of fetal cells, lung cancer cells
NNK in urine of children after prenatal and postnatal nicotine exposure
NNK also from oral nicotine (Hatsukami et al. 2004): aminoketone + NO
cell proliferation↑: AKT↑, XIAP↑, survivin↑, **apoptosis**↓ (Dasgupta 06)
β-arrestin: activation of Src & Rb–Raf-1 pathways, unregulated growth.
activation of protein kinase C: cancer migration, invasion (Xu & Deng 06)
nicotine: DNA adducts, genotoxic, proliferation, **angiogenesis**

ASH 2005: All forms of NRT can be used by smokers **aged 12 to 17 years** (for 12 weeks without a health care professional).

Recommendations driven by commercial interests?

Moolchan et al. 2005: Lack of evidence for effectiveness in adolescents.

Klesges et al. 2003: NRT used simultaneously. As a gateway drug to smoking.

In a study of 4,399 children aged 6 to 17 years, even the lowest exposure, as monitored by the levels of **cotinine** in blood, urine, saliva and hair, was found to significantly impair, in a dose-related manner, the children's **reading, math, and reasoning** scores (Yolton et al., 2005).

Early experimental nicotine exposure: irreversible effects on hippocampal structure, function, learning, and memory (Slotkin 2002).

Chronic prenatal nicotine exposure leads to increased mortality of newborn rats from hypoxic stress (Benowitz et al. 2004).

Possibly brainstem abnormality (more frequent in boys) with serotonin deficiency and parental smoking leads to **SIDS** (Paterson et al. 2006).

Coleman et al. 2005 recommend patch (8 weeks) for pregnant smokers
(Coleman et al. 2004 patch in 2 studies: quitrate like placebo!)

N I C O T I N E F O R T H E F E T U S ?

- reduces placental blood flow, accelerates fetal heart rate,
 - decreases fetal respiratory movements
 - inhibits aromatase, estrogen synthesis (maternal plasma levels ↓ 10%)
 - maturation of lung: fibroblasts → myofibroblasts (cell culture: nanomolar conc.)
children prone to lung infections, poor lung function, persisting?
fewer and larger alveoli (mediated by $\alpha 7 n A C h R s$ in lung cells)
- NRT use during the first 12 weeks of pregnancy increased congenital **malformations**: OR overall **1.6** (1.0-2.6), musculoskeletal **2.6** (1.5-4.5) in Danish birth cohort (Morales-Suarez-Varela et al. 06).

not typical as seen in children
of smoking mothers:



NICOTINE FOR THE FETAL BRAIN ?

In the developing nervous system nAChRs are expressed prior to the formation of the neurons which later establish synaptic contact with the nAChRs. By modifying the function of these receptors, nicotine can interfere with the normal developmental role of ACh (Falk et al. 2005). Inappropriate nicotinic stimulation ends cell proliferation prematurely, initiates cellular differentiation, resulting in a **reduced number of neurons** in selected areas of the brain (Slotkin 2006).

- Fetotoxicity and neuroteratogenicity can cause cognitive, affective, and behavioral disorders (as seen in children of smoking mothers).
- Neonatal nicotine exposure impairs central auditory processing and **auditory learning** in adult rats (Liang et al. 2006).
- Blocking of nAChRs in the developing **sensory cortex** during a critical period leads to permanent deficits (Metherate 04, Slikker et al. 05).
- Prenatal nicotine may also prime the brain for **depression** (Law et al.03), and for nicotine **addiction** (Abreu-Villaa et al. 04; O'Callaghan et al. 06).

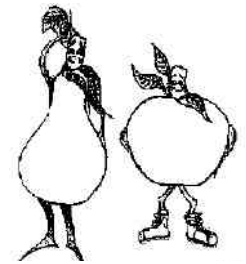
NRT: **weight** increase is not prevented but only postponed (Allen et al.2005)

Nicotine suppresses appetite (neuropeptide Y, leptine, insuline↑)in the beginning, but soon a new balance is reached and maintained until the smoker attempts to quit.

Cigarette smoking is associated with a lower BMI in adults over 24 y particularly in men, but not in younger people. In women, smoking is linked to the development of central adiposity (Akbartabartoori et al. 2005).

FOR GIRLS ONLY!

Gallaher / Austria Tabak bringt ein neues Produkt auf den österreichischen Markt. **Sobranie Pinks** ist der Name dieser „Slim-Zigarette“ (= Zigarette mit geringerem Durchmesser), die speziell für Frauen entwickelt wurde.



Nicotine (concentrated in gastric juice) promotes **gastritis & peptic ulcer**

(pepsinogen↑, vasopressine↑, prostaglandine E2↓, glutathione↓),

Nicotine promotes gastroesophageal **reflux** (NO release↑)

CONCLUSIONS: nicotine only on prescription, no advertising
licensing tobacco sales; long-term goal: removal from free
market

focus of tobacco control on prevention (prevent or delay start)

focus of therapy on counseling (pregnant women, children)



Ginzel et al. 2007: Nicotine for the Fetus, the Infant and the Adolescent?
Journal of Health Psychology 12, 2, 215-224.

Moshammer H, Neuberger M 2007: Long term success of short smoking
cessation seminars. Addict Behav 32,7,1486-1493.