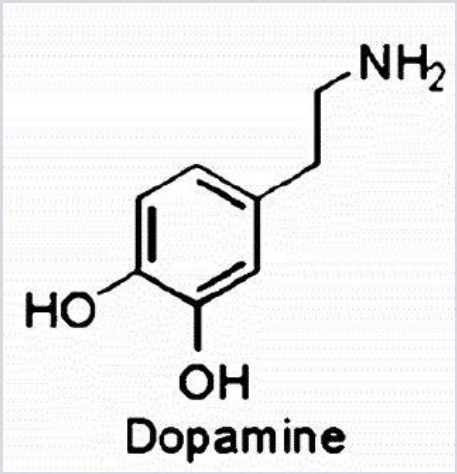
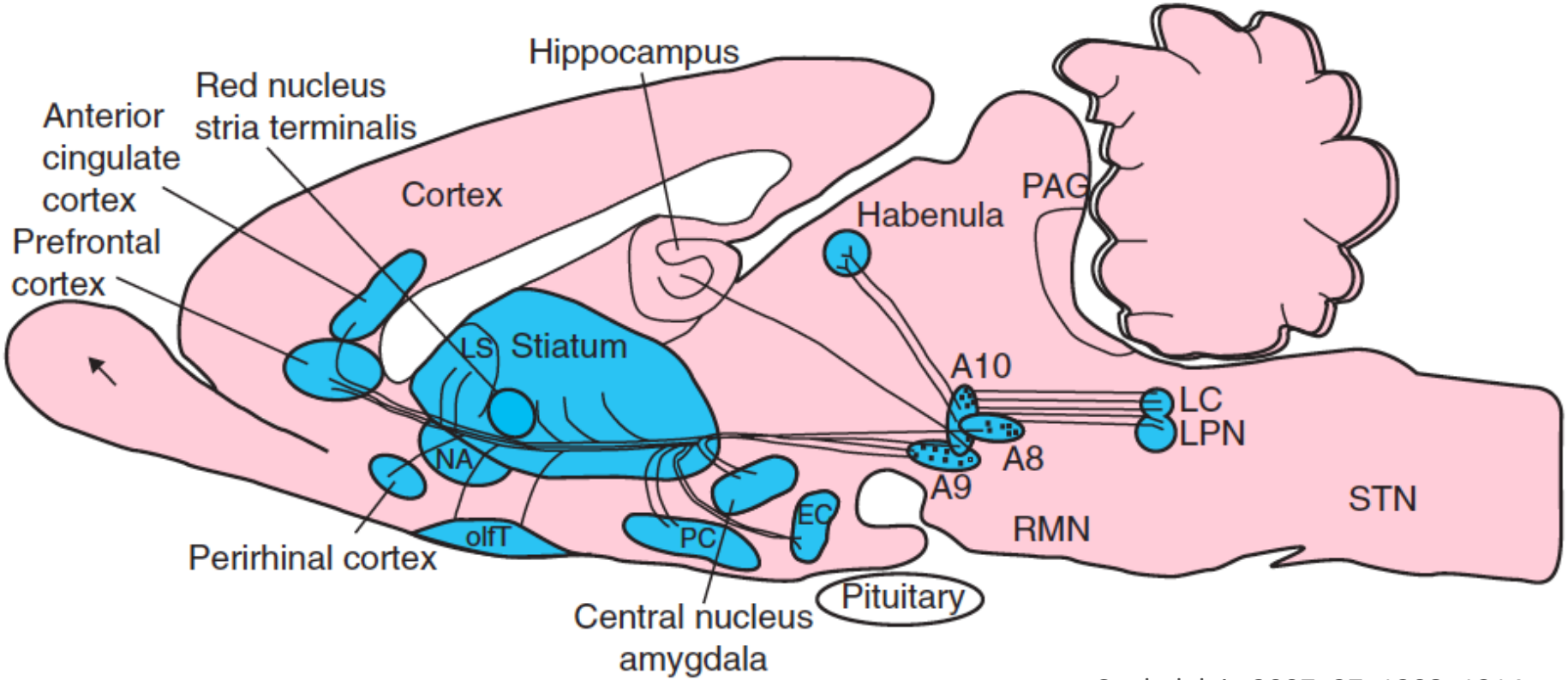
Dopamine & migraine

盧相如
小港醫院神經內科
2011.2.19



Major dopaminergic cell groups within brainstem

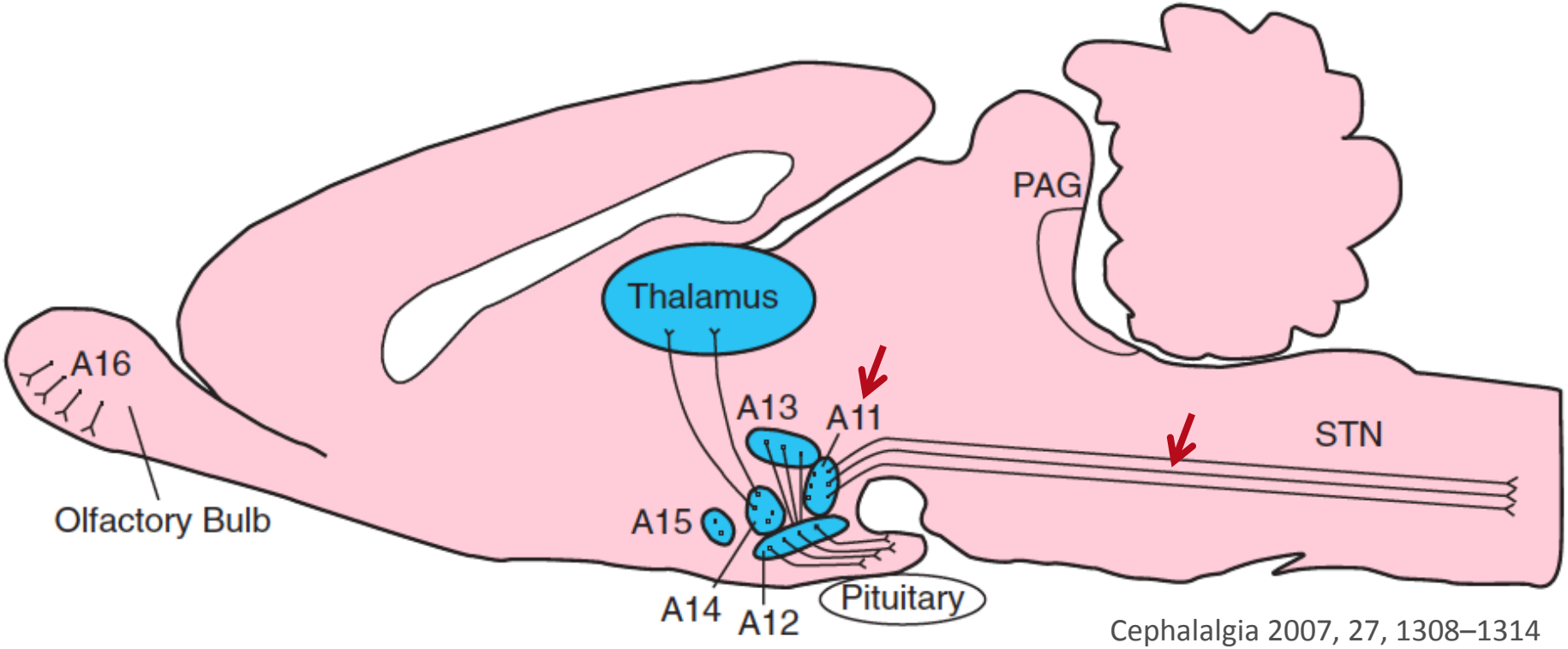


Cephalalgia 2007, 27, 1308–1314

A8-A10:

- **Nigrostriatal system: substantia nigra to the caudate-putamen (neostriatum) … related to movement and sensory stimuli**
- **Mesocorticolimbic system: ventral tegmentum to the mesolimbic forebrain … related to cognition, reward, emotional behavior**

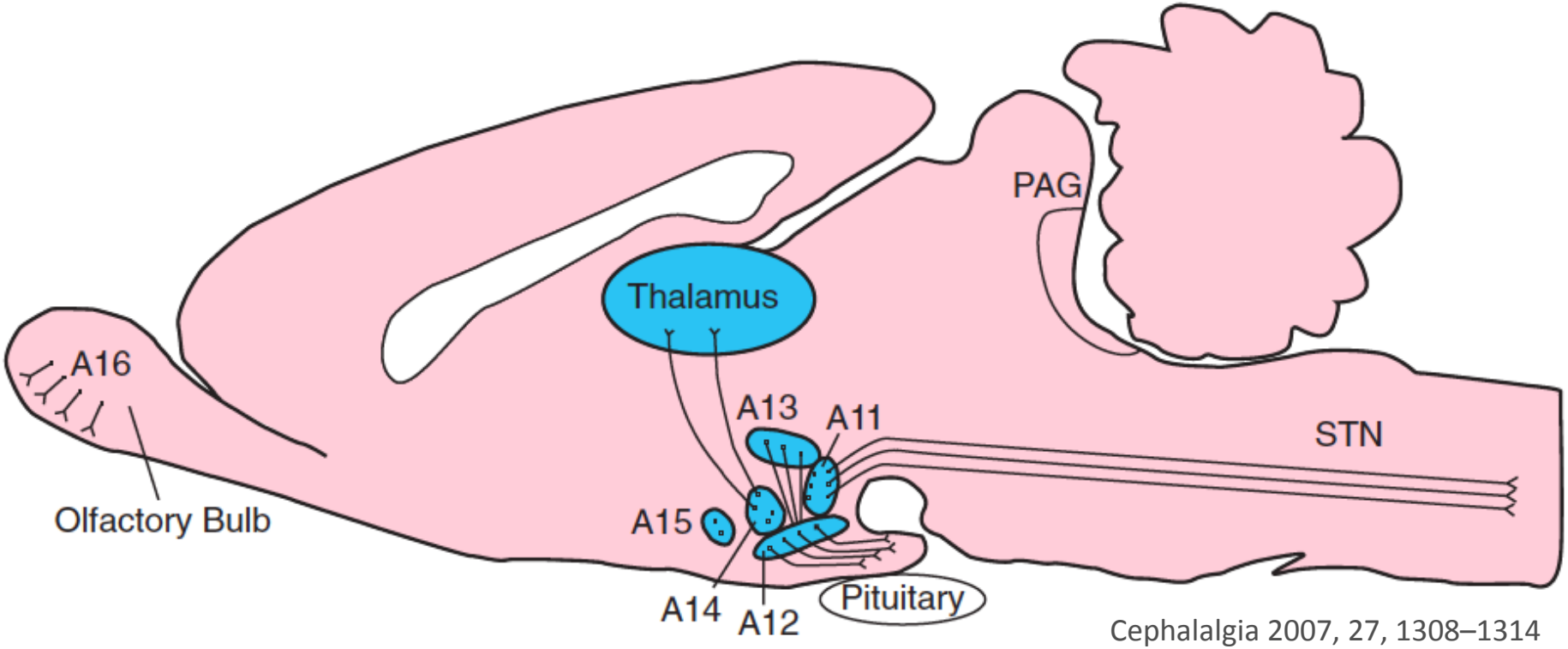
Major dopaminergic cell groups within brainstem



Cephalalgia 2007, 27, 1308–1314

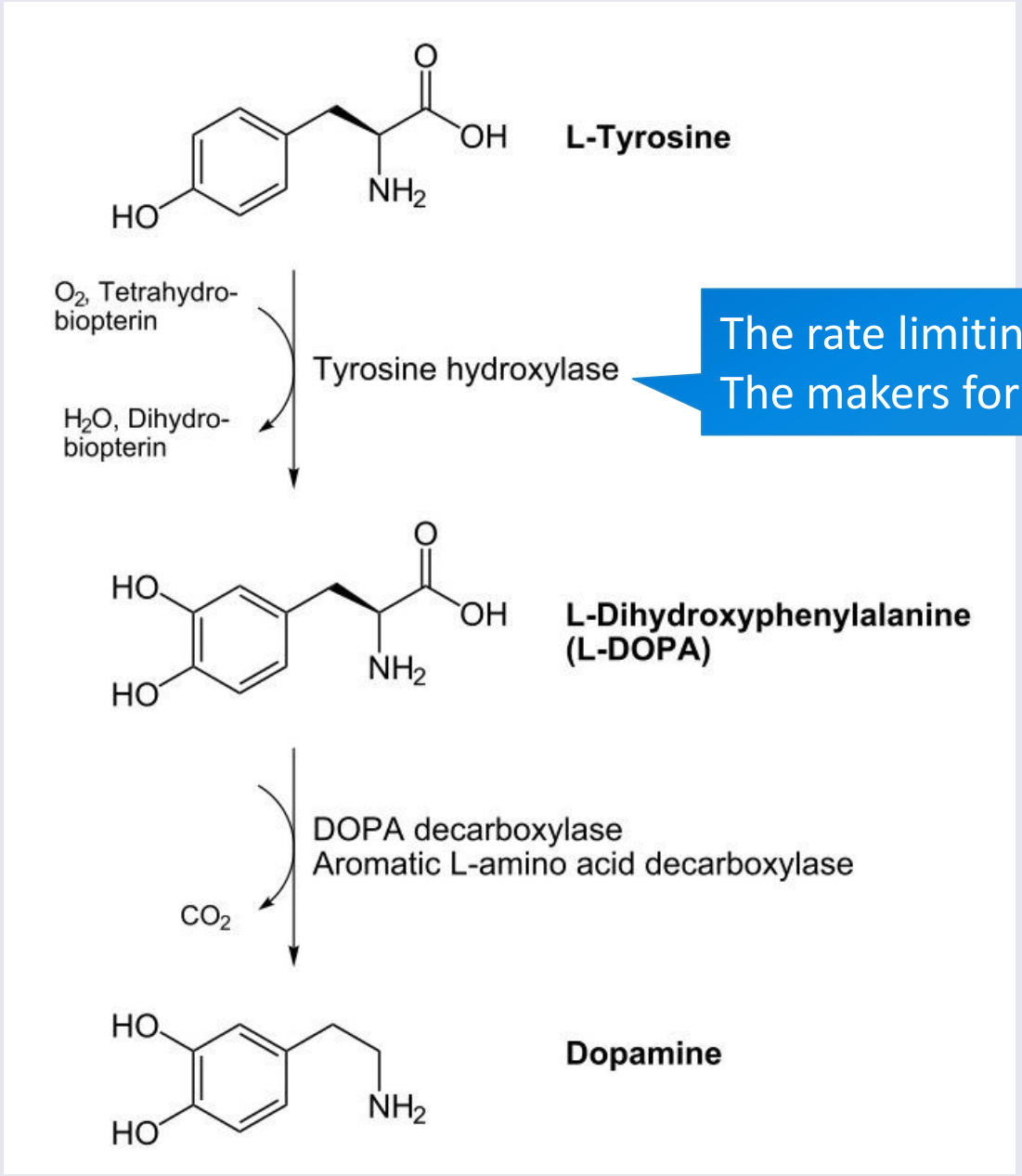
- A11: hypothalamic projections to the spinal cord dorsal horn
- The A12-14 diencephalic cell groups: tuberoinfundibular & tuberohypophysial pathways

Major dopaminergic cell groups within brainstem



Cephalalgia 2007, 27, 1308–1314

- A15 includes cells in hypothalamus, and dorsal and ventrolateral preoptic area
- A16 is the olfactory bulb
- A17 (not shown): retinal dopaminergic neurons

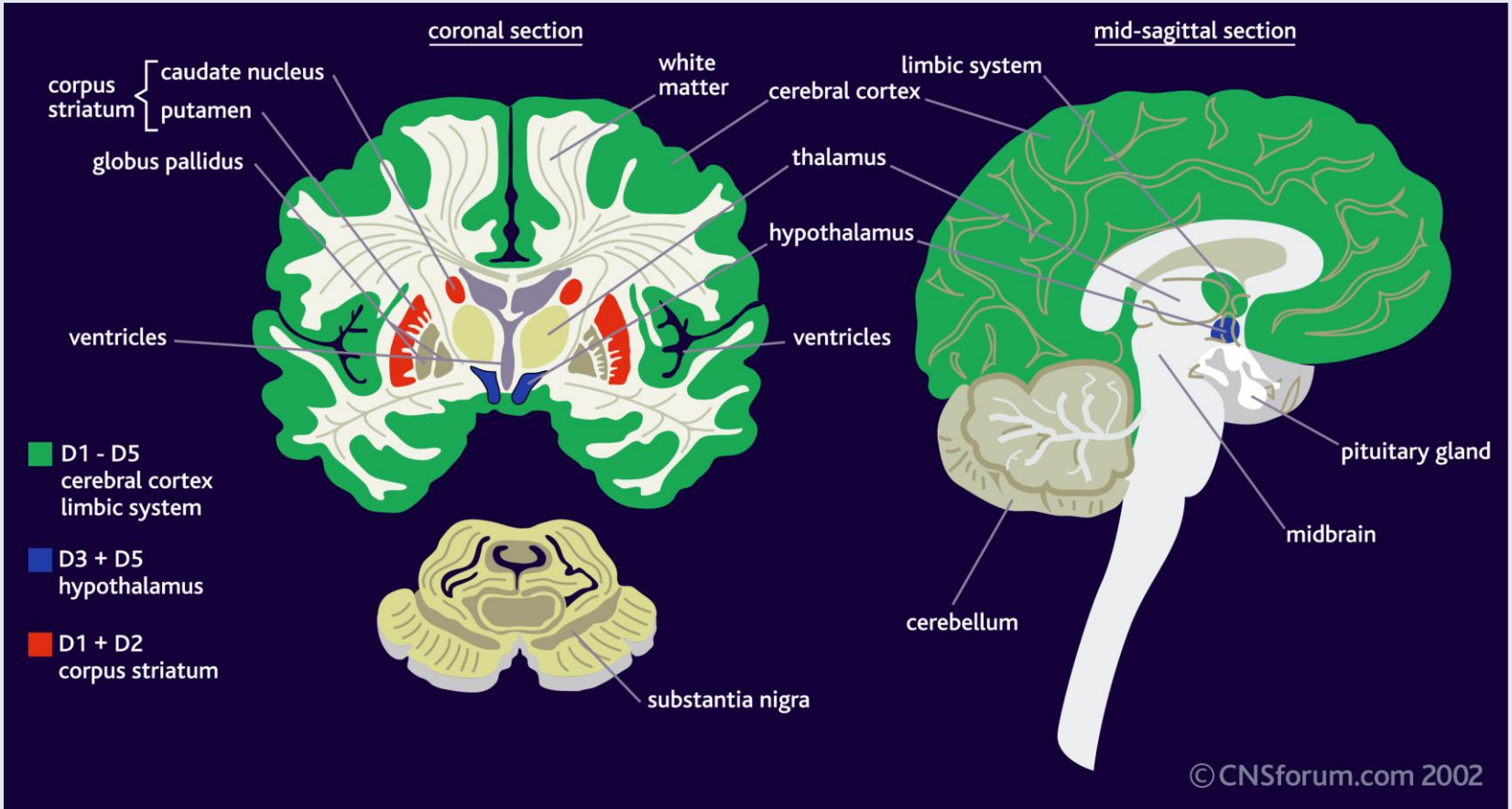


The rate limiting enzyme
The makers for dopaminergic neurons

file:///Users/srlu/Downloads/Catecholamines_biosynthesis.svg

Dopamine receptors

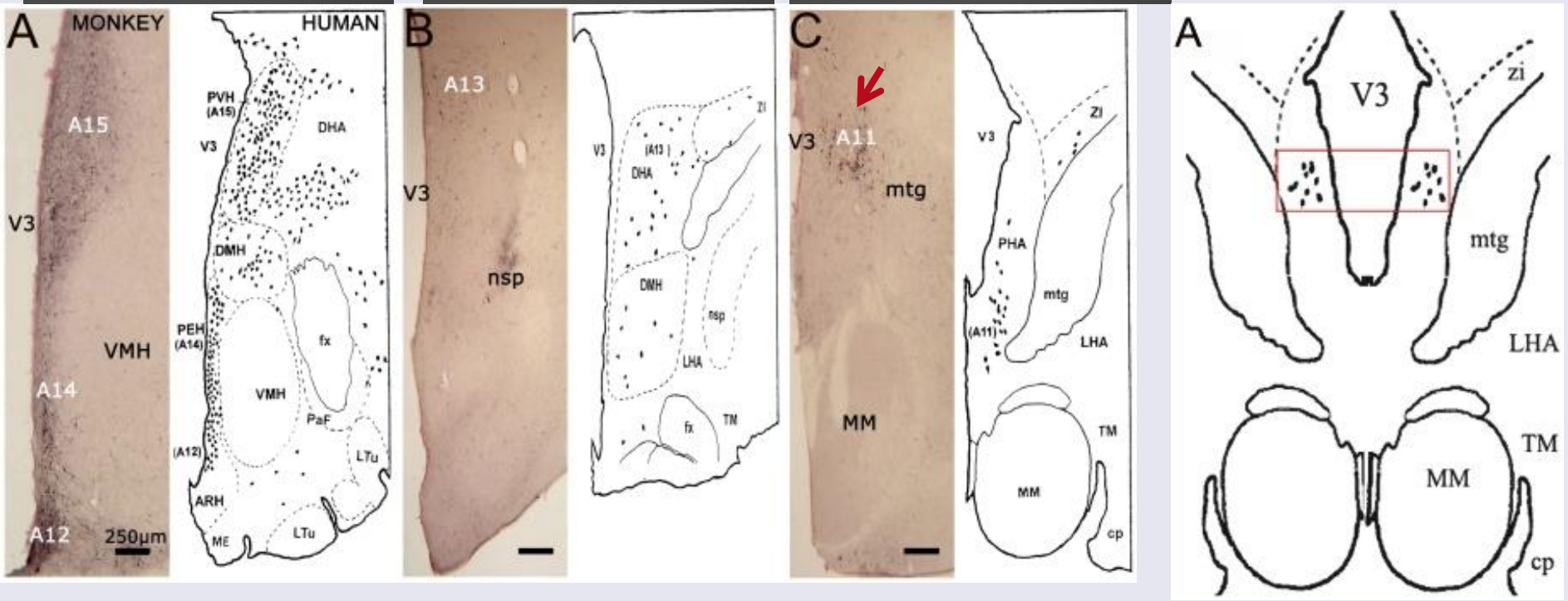
- D1/D5: activate adenylyl cyclase, ↑cAMP
- D2/D3/D4: inhibit adenylyl cyclase, ↓cAMP



Hypothalamic A11 dopaminergic nucleus

- First identified by Dahlstrom & Fuxe in 1960s
- Send direct inhibitory projections to the spinal cord dorsal horn (the sole source of dopamine in the spinal cord)

Anterior hypothalamus | Middle hypothalamus | Posterior hypothalamus



Tyrosine hydroxylase-positive (DA) neurons within the diencephalon:

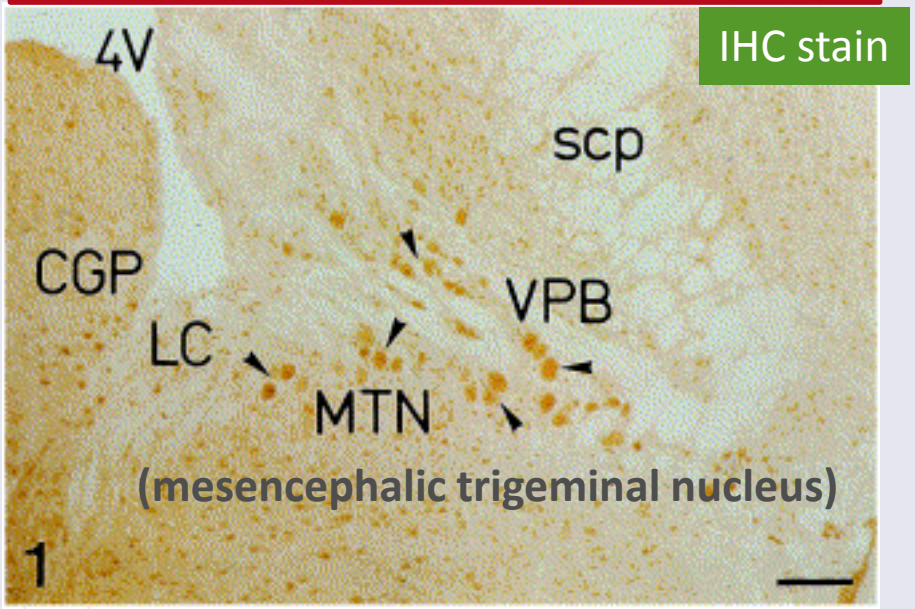
A11 nuclei are distributed along the rostrocaudal axis, in the periventricular posterior region of hypothalamus and periventricular grey of the caudal thalamus

PLoS ONE 2010; 5(10): e13306

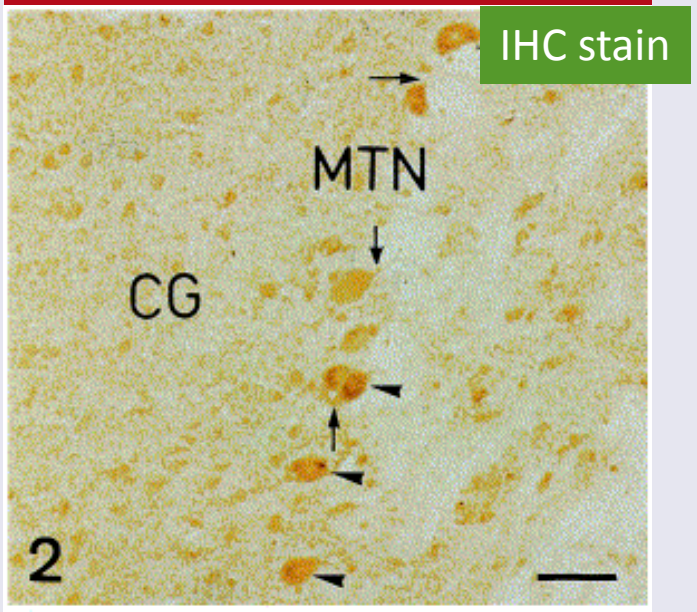
Dopamine in trigeminocervical complex (TCC):

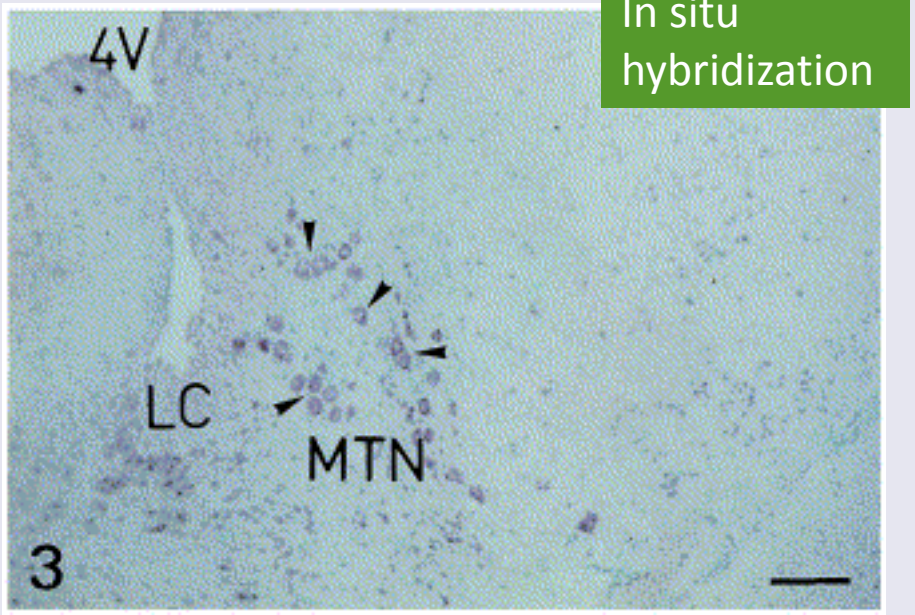
- D1/D2 receptors exist in trigeminal ganglion and spinal trigeminal nucleus:
  - D1 receptors in deeper laminae
  - D2 receptors laminae I/IIo
- Microinjection of DA: ↓firing rate of activated neuron in the TCC
- Electric stimulation of the A11 nucleus: ↓evoked nociceptive signaling from TCC (this effect is reversed by D2 antagonists)
- Electrical lesioning of the A11 nucleus: ↑evoked nociceptive signaling from TCC; ↑response to non-nociceptive stimuli
- IV CNS-active D2 antagonists: ↑TCC firing
  IV PNS-active D2 antagonists (domperidome): no effect on TCC

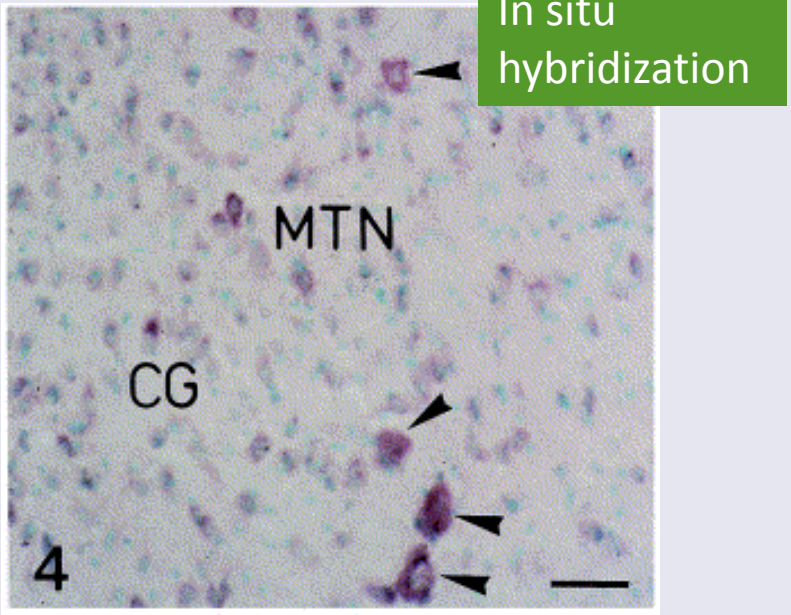
Caudal MTN



Rostral MTN



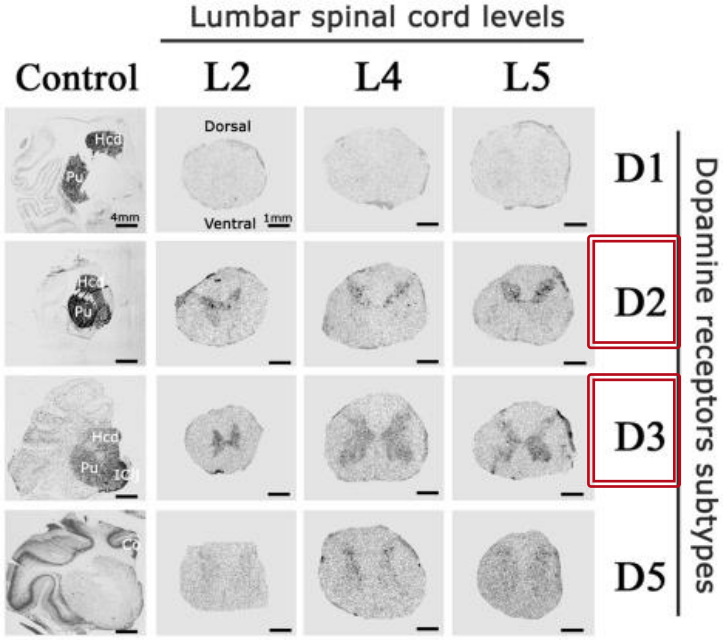




Neuroscience Letters 236 (1997) 83–86

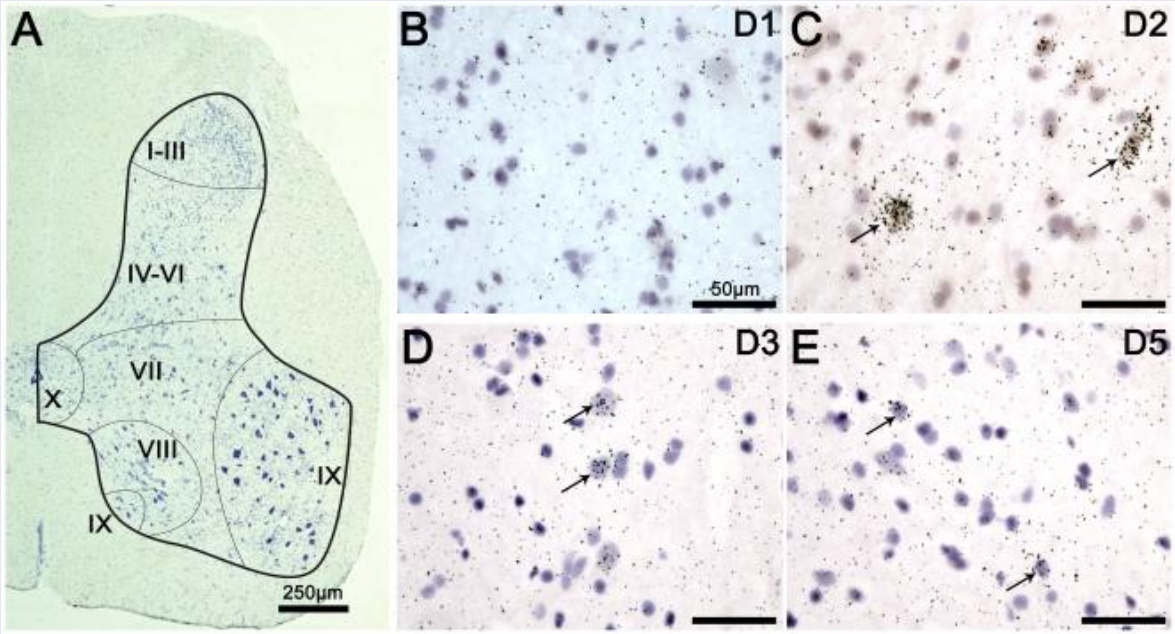
Dopamine in the spinal cord:

- DA contributes to spinal reflex excitability where it depresses monosynaptic ‘‘stretch’’ reflexes via D2 and D3 receptors
- DA reduces the behavioral responses to noxious stimulation in rodents
- DA turnover in the spinal dorsal horn increases in response to noxious stimuli
- Spinal release of DA activate spinal motor networks involved in locomotion



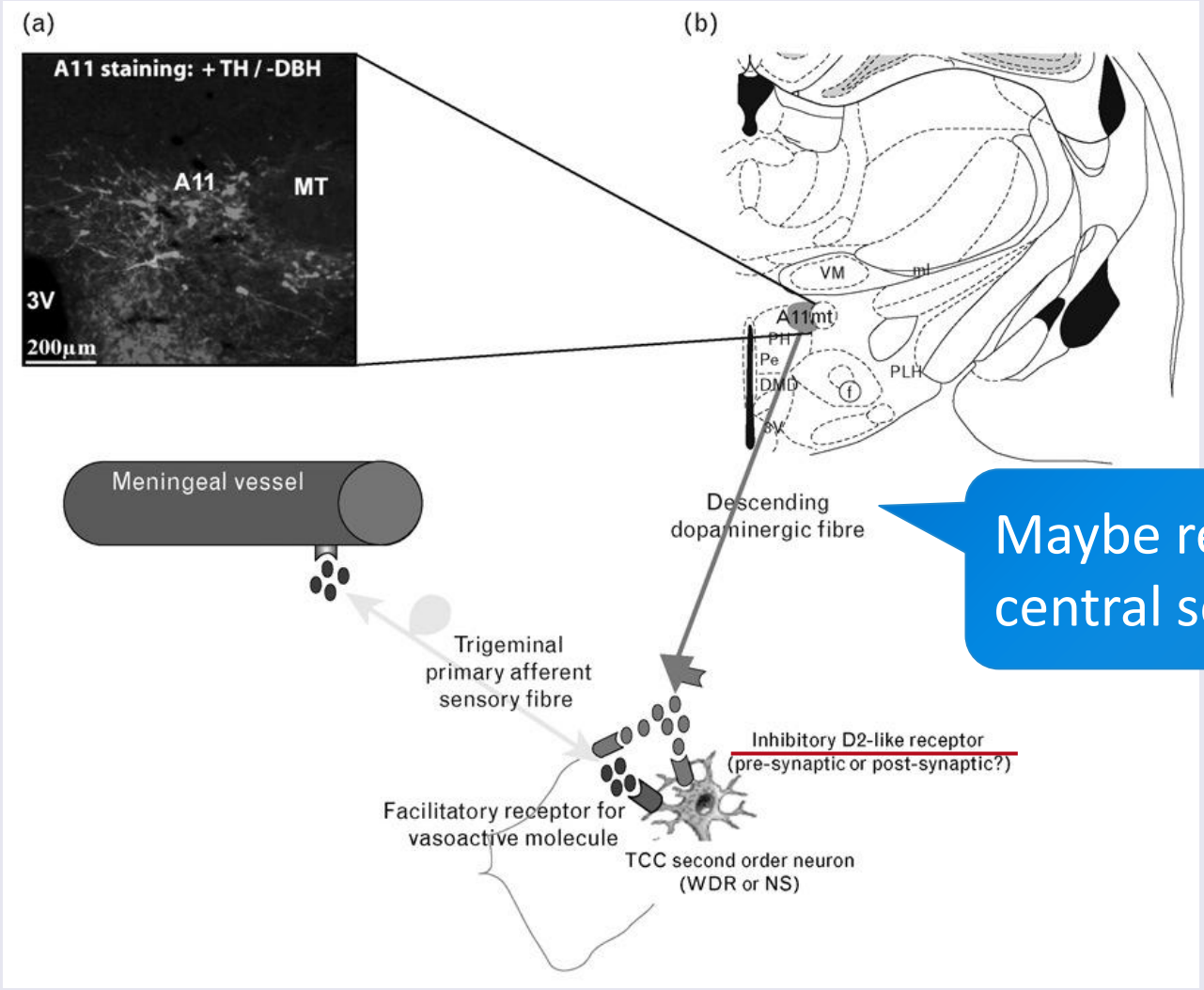
Microscopic detection of D2, D3 and D5 dopaminergic receptors in the lumbar cord.

D2 labeling was mainly found in laminae I to VI, that the D3 labeling showed a wider distribution in laminae I to X.



PLoS ONE 2010; 5(10): e13306

Current Opinion in Neurology 2010, 23:275–281



Maybe related to central sensitization?

It is proposed that when the TCC is activated, **the A11 nucleus provide inhibitory DA to D2-like receptors** at either presynaptic first-order neurons or post-synaptic second-order neurons in the TCC.

The connection between dopamine and migraine

- The premonitory symptoms of migraine
- Dopamine pharmacotherapy
- Dopamine and migraine comorbidity
- Dopamine genetics and migraine

Dopamine pharmacotherapy

- No strong evidence suggests that dopamine agonists can induce migraine
- Dopamine D2 antagonists can relieve migraine:
  - prochlorpromazine, prochlorperazine, metoclopramide, droperidol, haloperidol, domperidone
  - Mechanism: uncertain

  (Remember: not all these D2 antagonists have exclusively DA pharmacology)

Premonitory symptoms of migraine and dopamine

- **Premonitory Sx** include: yawning, drowsiness, mood change, irritability…

- **In migraineurs**:
  - Apomorphine (DA agonist): ↑yawning, N/V
  - D2 antagonists: ↓yawning, antiemetic
  - MAO-B inhibitor: ↓↓[prolactin], esp. in follicular phase
  - Monoamine depletors: ↑↑[prolactin]

- **In rats**:
  - ↑yawning by central D2 agonists (not D1)
    ↓yawning by both D1/D2 antagonists
  - Peripheral D2 antagonists: no effect on yawning
  - Dopamine agonists: ↑hyperactivity & irritability

Dopamine and migraine comorbidity

- 1. Restless leg syndrome
- 2. Ovarian hyper-stimulation syndrome
- 3. menstrual migraine

1. Restless leg syndrome (RLS)

- A sensorimotor disorder characterized by uncomfortable/unpleasant sensations in the limbs, relieved by movement and worsened during periods of inactivity
- Hypothalamus **A11 nucleus** is primarily known for a possible role in RLS
  - Dopamine D2 agonists relieve the Sx of RLS
  - Dopamine D2 antagonists aggravate the Sx of RLS
- A comorbidity of migraine and RLS has been reported

Table 1 Demographic and clinical data of the headache patients and control subjects (presented as arithmetic mean and SD or as percentage)

	Headache patients (n=200)	Control subjects (n=120)	*p*-value
Age (years)	37.2±11.1 (18–65)	37.2±8.5 (20–56)	NS
Female age	37.6±11.5 (18–65) (n=149)	36.7±8.1 (20–53) (n=90)	NS
Male age	36.1±10.0 (21–59) (n=51)	38.8±9.6 (20–56) (n=30)	NS
Headache age at onset	22.9±9.4 (8–60)	NA	NA
Headache duration	14.3±10.1 (1–40)	NA	NA
Attack frequency per month	Low (<1/month): 41.0% Medium: (1–3/month): 20.5% High (>3/month): 38.5%	NA	NA
Intensity of pain	Mild: 9.5% Moderate: 50.5% Severe: 40.0%	NA	NA
RLS prevalence	22.4% (n=44)	8.3% (n=10)	0.002
Sex-Female	84.1% (n=37)	80.0% (n=8)	NS
Sex-Male	15.9% (n=7)	20.0% (n=2)	
RLS age at onset (years)	33.23±8,4	29.40±6.,83	0.187
RLS duration (years)	5.6±4.5 (1–20)	4.6±3.1 (1–10)	0.520

NA, not applicable

- 200 headache patients and 120 sex- and age-matched controls.
- The prevalence of RLS is higher in headache patients (22.4%).
- More than 60% of RLS patients were affected by MO and 30% (n=13) by mixed headache types (MA/MO/ETTH).
- Headache patients with RLS reported sleep disturbances more frequently than did those without RLS (50.0% vs 32.7%).

d'Onofrio et al. Neurol Sci (2008) 29:S169–S172

Table 1 Demographics and the clinical data of restless legs syndrome (RLS) among patients with different headache disorders

	Total (N=1041)	Migraine (N=772)	Tension-type headache (N=218)	Cluster headache (N=51)	p Value
Total subjects					
Mean age (years)	43.7±14.4	42.1±13.3	50.6±16.2	38.4±12.6	<0.001
Female patients, n (%)	801 (76.9%)	644 (83.4%)	146 (67.0%)	11 (21.6%)	<0.001
Mean BMI, kg/m^2	23.1±3.6	22.9±3.7	23.5±2.9	24.7±3.6	<0.001
RLS, n (%)	99 (9.5%)	88 (11.4%)	10 (4.6%)	1 (2.0%)	0.002
Clinically relevant RLS, n (%)	37 (3.6%)	33 (4.3%)	3 (1.4%)	1 (2.0%)	0.39
RLS subjects only					
Mean International RLS Study Group Rating Scale	12.1±7.6	12.3±7.5	10.0±8.7	14	0.64
Mean Hospital Anxiety and Depression Scale score	16.5±7.5	16.7±7.9	15.1±3.2	13	0.75
Pittsburgh Sleep Quality Index mean global sore	11.1±4.0	11.1±4.1	11.3±3.6	9	0.86
RLS with nocturnal leg jerks during sleep, n (%)	42 (42.4%)	38 (43.2%)	4 (40.0%)	0 (0%)	0.68
Clinically relevant RLS, n (%)	37 (37.4%)	33 (37.5%)	3 (30%)	1 (100%)	0.39
Family history of RLS, n (%)	17 (17.2%)	15 (17.0%)	2 (20.0%)	0 (0%)	0.88
Willingness to treat; n (%)	56 (57.1%)	49 (56.3%)	6 (60.0%)	1 (100%)	0.67

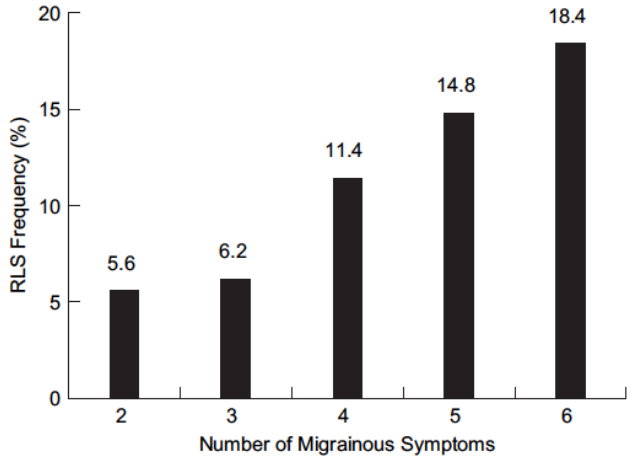


Figure 1 Relationship between the frequencies of restless legs syndrome (RLS) and the number of migrainous symptoms (unilateral, throbbing, aggravation by physical activities, moderate or severe intensity, nausea/vomiting, photophobia and phonophobia) in patients with migraine ($p<0.001$, linear-by-linear association).

The frequencies of RLS in migraineurs (11.4%) was higher than in those with TTH or CH.

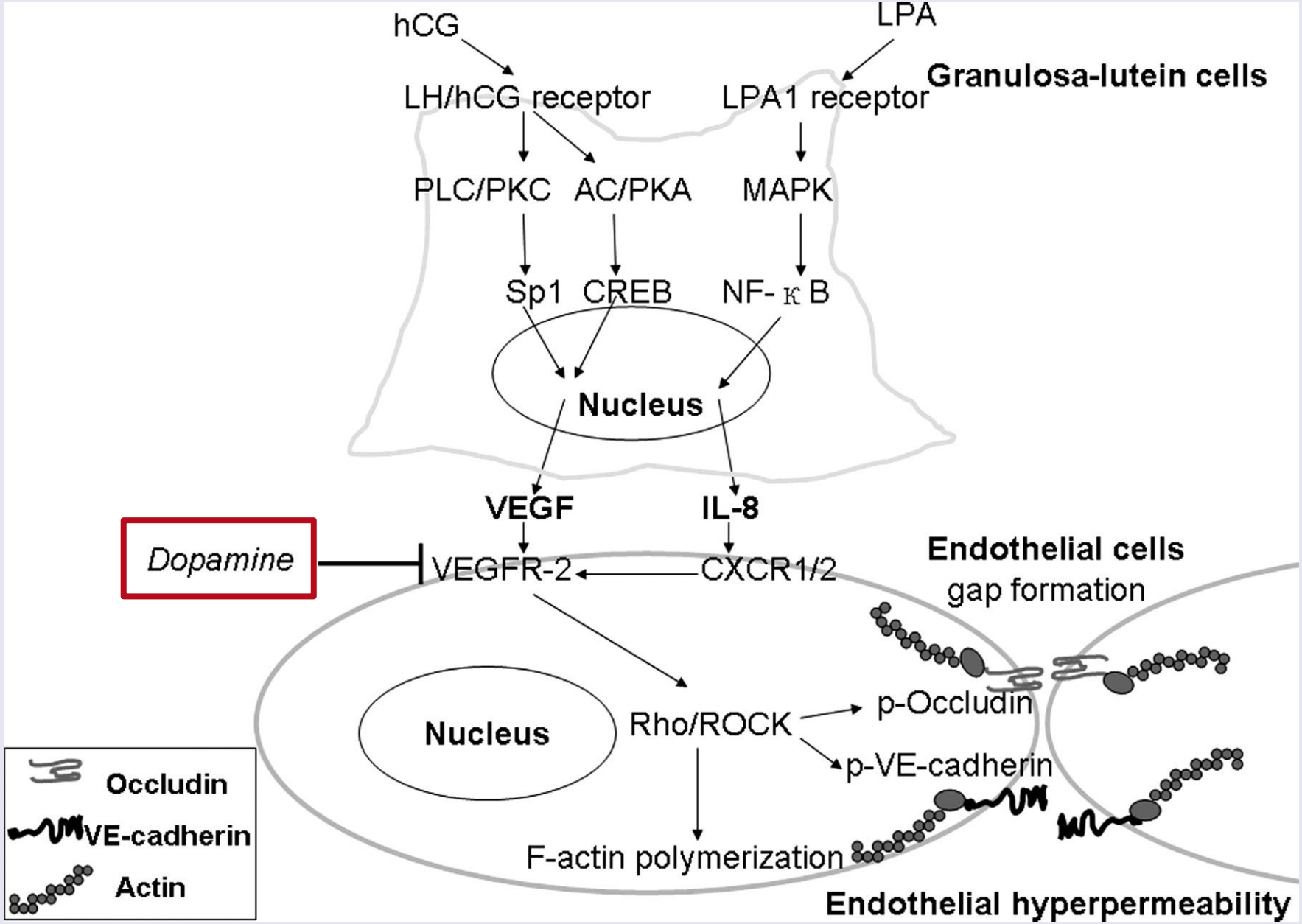
In migraine patients, comorbidity with RLS was associated with higher frequencies of photo-/phono-phobia, exacerbation by physical activities, vertigo, dizziness, tinnitus and neck pain, and higher scores of MIDAS & HADS.

J Neurol Neurosurg Psychiatry 2010;81:524-528.

2. Ovarian hyper-stimulation syndrome (OHSS)

- A rare but potentially life-threatening condition
- After fertility treatment: ↑capillary permeability → dramatic fluid shift from vascular to 3rd space of the abdomen and pleura
- DA agonists improves the markers of permeability in OHSS, mainly via its inhibitory effect on the common VEGFR-2 signaling.
- In a recent case-control trial, migraine is associated with increased risk of OHSS (OR = 4.18-4.78).

VEGFR = vascular endothelial growth factor receptor



Human Reproduction, Vol.25, No.3 pp. 757–767, 2010

TABLE 1

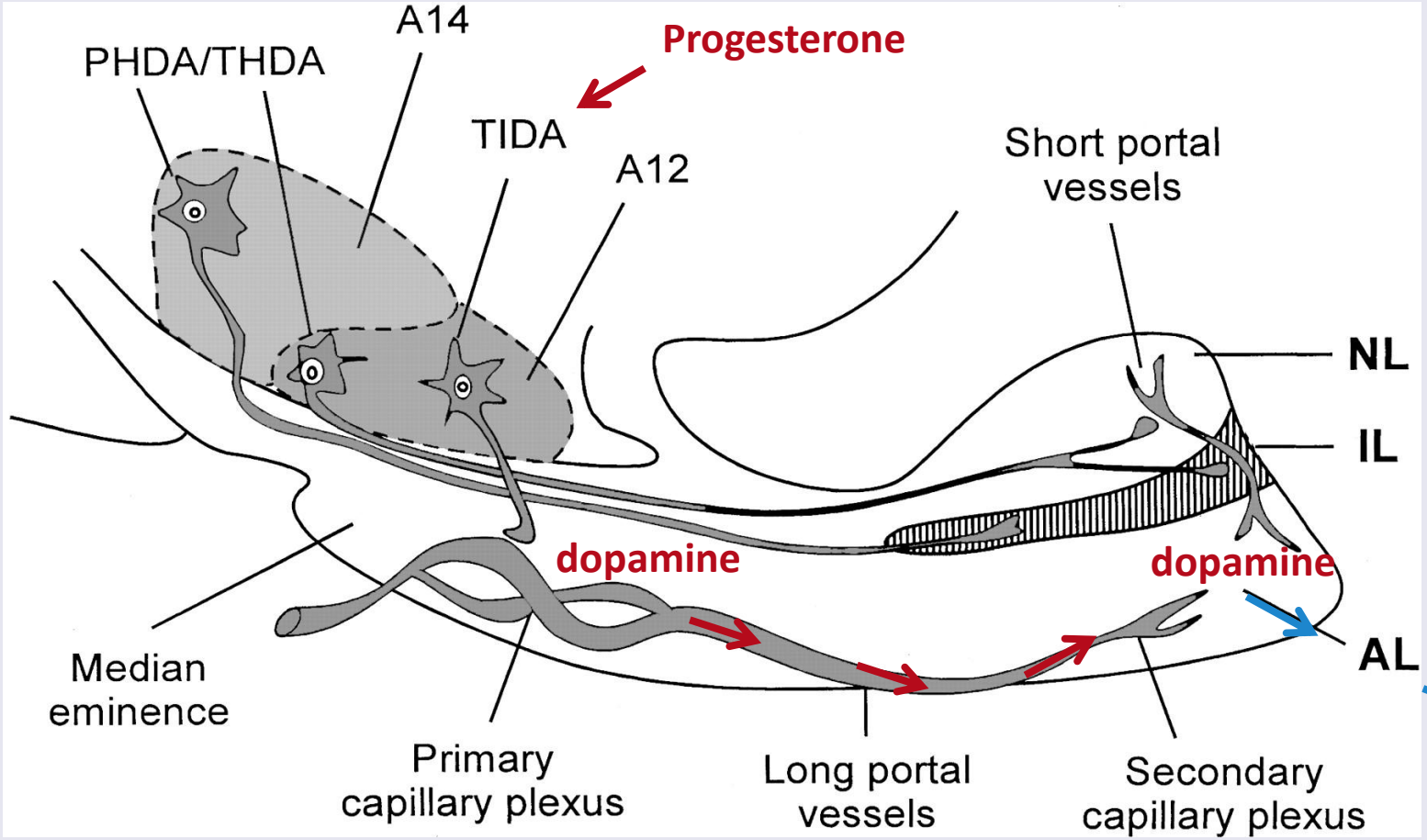
Analysis of potential predictors of OHSS.

Risk factor (full model)	Cases (N = 135) N	Cases (N = 135) Summary	Controls (N = 270) N	Controls (N = 270) Summary	OR (95% CI)	*P* value
Age (y)	135	30.6 ± 3.8	270	32.0 ± 4.2	0.92 (0.88–0.97)	.003
BMI (kg/m^2)	135	26.1 ± 6.9	270	26.1 ± 6.3	1.00 (0.97–1.04)	.91
Race (white)	126	115 (91.3)	261	234 (89.7)	1.28 (0.62–2.64)	.51
Nulligravid (%)	135	80 (59.3)	270	159 (58.9)	1.02 (0.66–1.57)	.94
Day 3 FSH (IU/L)	68	6.3 ± 2.6	183	7.2 ± 3.4	0.85 (0.75–0.96)	.01
Antral follicle count	85	30.6 ± 13.2	138	20.8 ± 11.2	1.09 (1.05–1.14)	< .001
PCOS (%)	135	70 (51.8)	270	55 (20.4)	3.88 (2.46–6.13)	< .001
Migraine history (%)	135	47 (34.8)	270	32 (11.8)	4.78 (2.63–8.66)	< .001
Uterine stripe (mm)	127	11.3 ± 2.5	263	11.6 ± 2.7	0.97 (0.88–1.06)	.50
Multiple gestation (%)	135	31 (23.0)	270	37 (13.7)	1.97 (1.12–3.44)	.02

Risk factor (IVF only)	Cases (N = 111) N	Cases (N = 111) Summary	Controls (N = 222) N	Controls (N = 222) Summary	OR (95% CI)	*P* value
Age (y)	111	30.9 ± 3.8	222	31.8 ± 4.2	0.95 (0.89–1.00)	.05
BMI (kg/m^2)	110	25.3 ± 5.9	220	26.0 ± 6.1	0.98 (0.94–1.02)	.33
Race (white)	105	95 (90.5)	215	192 (89.3)	1.20 (0.55–2.60)	.65
Nulligravid (%)	111	65 (58.6)	222	131 (59.0)	0.98 (0.60–1.60)	.93
Day 3 FSH (IU/L)	56	6.6 ± 2.6	147	7.2 ± 2.8	0.86 (0.74–0.99)	.04
Antral follicle count	75	30.1 ± 13.2	125	21.3 ± 11.3	1.09 (1.05–1.13)	< .001
PCOS (%)	111	50 (45.1)	222	43 (19.4)	3.09 (1.89–5.07)	< .001
Migraine history (%)	111	38 (34.2)	222	27 (12.2)	4.18 (2.24–7.83)	< .001
Uterine stripe (mm)	105	11.8 ± 2.3	222	12.0 ± 2.5	0.98 (0.88–1.08)	.63
Total FSH used (IU)	102	2,128 ± 1,204	221	3,096 ± 1,705	0.95 (0.92–0.97)	< .001
Stimulation days	99	10.4 ± 1.3	222	10.3 ± 1.5	1.02 (0.86–1.20)	.84
Peak E_2 (pg/mL)	105	3,258 ± 2,016	221	2,035 ± 1,232	1.07 (1.05–1.10)	< .001
No. of follicles	97	34.2 ± 12.9	213	18.8 ± 10.6	1.12 (1.08–1.16)	< .001
No. of embryos	103	13.0 ± 6.6	205	7.5 ± 4.6	1.19 (1.12–1.27)	< .001
Multiple gestation (%)	111	27 (24.3)	222	35 (15.8)	1.79 (0.99–3.24)	.06

Menstrual migraine and dopamine

- A drop in progesterone level at the end of luteal phase/start of follicular phase might trigger a migraine attack
- One study:
  - Migraine women have ↑prolactin levels
  - Cabergoline (D2 agonist) 0.5mg BIW improves the headache
- Hypothesis: ↓progesterone ⇒↓DA ⇒↑prolactin



Inhibition of prolactin release

PHDA = periventricular-hypophysial dopaminergic
TIDA = tuberoinfundibular dopaminergic
THDA = tuberohypophysial dopaminergic

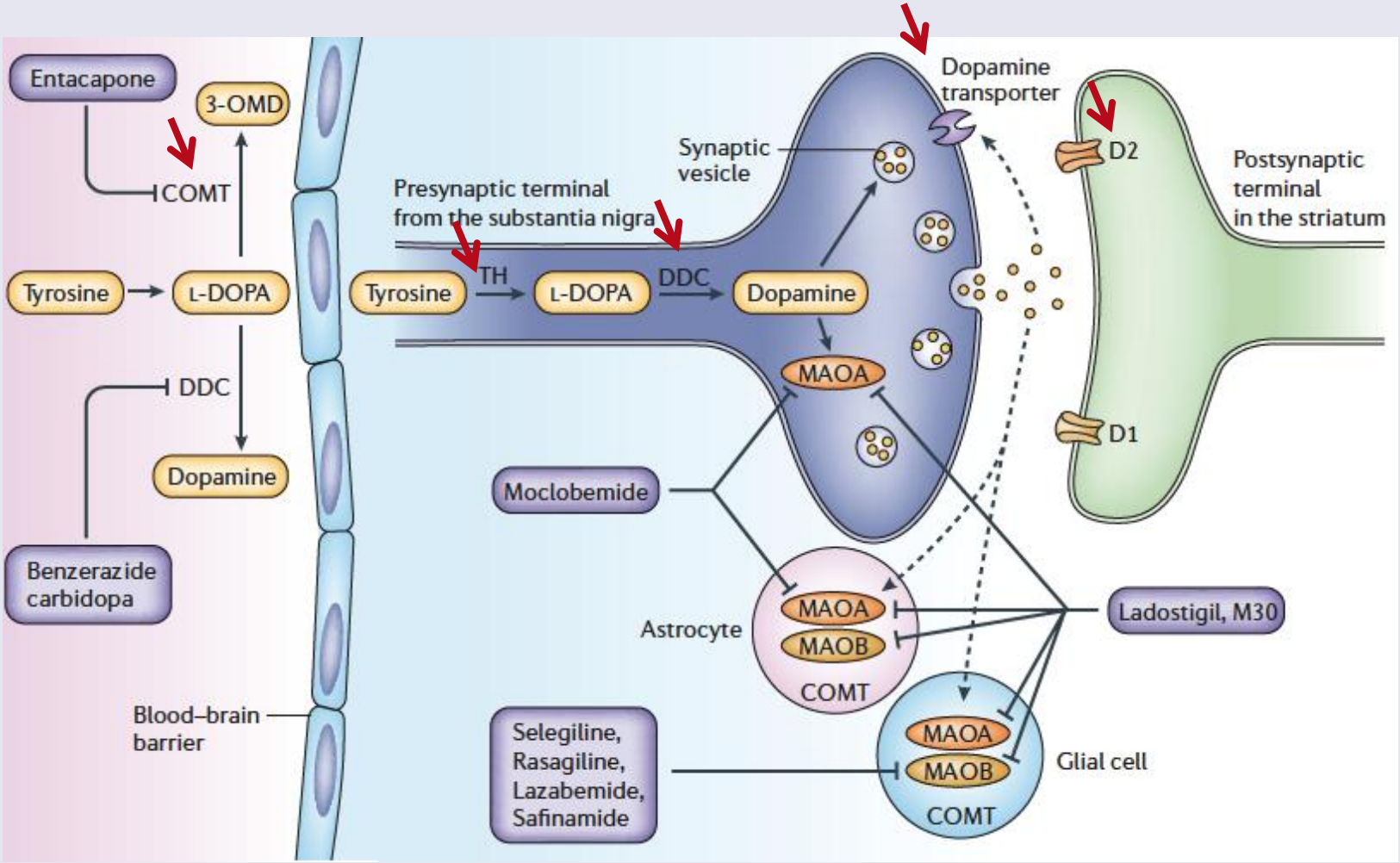
Endocr. Rev. 2001 22: 724-763

Dopamine and migraine comorbidity: summary

- 1. Restless leg syndrome
- 2. Ovarian hyper-stimulation syndrome
- 3. menstrual migraine
- 4. common migraine(?)

- All these disorders are probably related to ↓dopamine activity
- However, it still cannot explain why anti-DA can abort acute migraine

Dopamine genetics and migraine：targets



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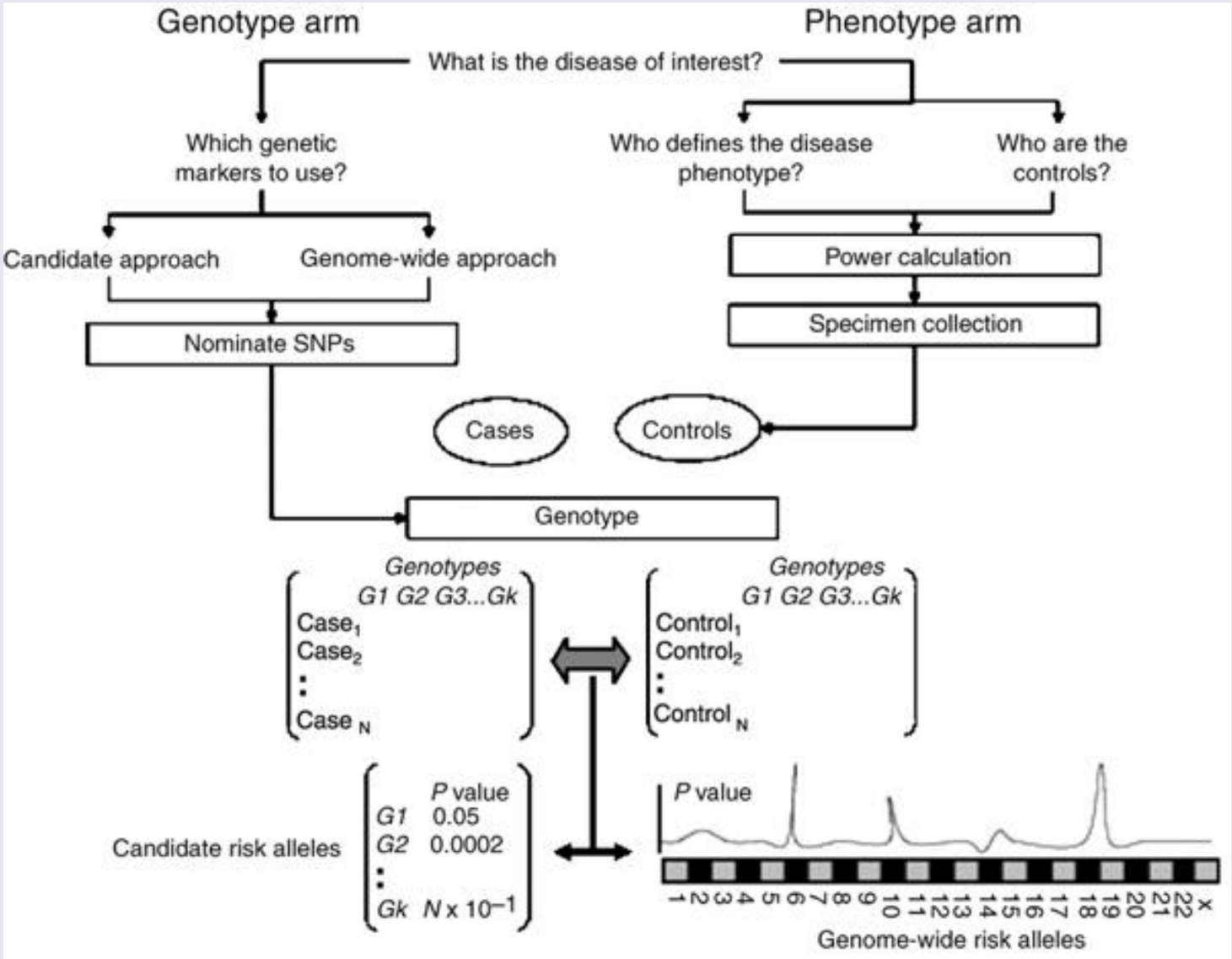
Genotype arm
Phenotype arm
What is the disease of interest?
Which genetic markers to use?
Who defines the disease phenotype?
Who are the controls?
Candidate approach
Genome-wide approach
Power calculation
Specimen collection
Nominate SNPs
Cases
Controls
Genotype
Genotypes
G1 G2 G3...Gk
Case1
Case2
Case N
Genotypes
G1 G2 G3...Gk
Control1
Control2
Control N
Candidate risk alleles
P value
G1 0.05
G2 0.0002
Gk N x 10−1
P value
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 x
Genome-wide risk alleles

Summary of genetic association studines for migraine (only n≥275 included)

Gene	DNA variatns	Associated allele with phenotype	authors
COMT	c.273A>G (Val158Met)	NS	Hagen 2006
DBH	-1021C>T +1603C>T	-1021T: P = 0.004 (P = 0.011/NS) NS (NS/NS)	Fernandez 2009
DBH	c.1434 + 1579A>G (rs2097629; intron 9)	c.1434 + 1579G: – (P = 0.01/–)	Todt 2009
DRD2	C.-32 + 16024T>G (rs7131056; intron 1)	C. -32 + 16024T – (p =0.006/-)	Todt 2009
SLC6A3	c.1840-204G>A (rs40184; intron 14)	c. 1840-204A – (p=0.03/-)	Todt 2009
SLC6A3	VNTR in intron 8	NS (NS/NS)	McCallum 2007

Hum Genet (2009) 126:115–132

Two-stage case-control genetic association study of dopamine-related genes: COMT, DBH, DDC, DRD1-5, SLC6A3, TH

Germany

Hum Genet (2009) 125:265–279
DOI 10.1007/s00439-009-0623-z

ORIGINAL INVESTIGATION

New genetic evidence for involvement of the dopamine system in migraine with aura

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Abstract In order to systematically test the hypothesis that genetic variation in the dopamine system contributes to the susceptibility to migraine with aura (MA), we performed a comprehensive genetic association study of altogether ten genes from the dopaminergic system in a large German migraine with aura case-control sample. Based on the genotyping results of 53 variants across the ten genes in 270 MA cases and 272 controls, three genes—*DBH*, *DRD2* and *SLC6A3*—were chosen to proceed to additional genotyping of 380 MA cases and 378 controls. Four of the 26 genotyped polymorphisms in these three genes displayed nominally significant allelic *P*-values in the sample of 650 MA patients and 650 controls. Three of these SNPs [rs2097629 in *DBH* (uncorrected allelic *P* value = 0.0012, OR = 0.77), rs7131056 in *DRD2* (uncorrected allelic *P* value = 0.0018, OR = 1.28) and rs40184 in *SLC6A3* (uncorrected allelic *P* value = 0.0082, OR = 0.81)] remained significant after gene-wide correction for multiple testing by permutation analysis. Further consideration of imputed genotype data from 2,937 British control individuals did not affirm the association with *DRD2*, but supported the associations with *DBH* and *SLC6A3*. Our data provide new evidence for an involvement of components of the dopaminergic system—in particular the dopamine-beta hydroxylase and dopamine transporter genes—to the pathogenesis of migraine with aura.

Introduction

Migraine is a common and genetically complex disorder. Family and twin studies provide convincing evidence that hereditary factors contribute significantly to its etiology (Palotie and Wessman 2002). The genetic influence seems

U. Todt and C. Netzer contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00439-009-0623-z) contains supplementary material, which is available to authorized users.

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Two-stage case-control association study of dopamine-related genes and migraine

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Abstract

Background: We previously reported risk haplotypes for two genes related with serotonin and dopamine metabolism: *MAOA* in migraine without aura and *DDC* in migraine with aura. Herein we investigate the contribution to migraine susceptibility of eight additional genes involved in dopamine neurotransmission.

Methods: We performed a two-stage case-control association study of 50 tag single nucleotide polymorphisms (SNPs), selected according to genetic coverage parameters. The first analysis consisted of 263 patients and 274 controls and the replication study was composed by 259 cases and 287 controls. All cases were diagnosed according to ICHD-II criteria, were Spanish Caucasian, and were sex-matched with control subjects.

Results: Single-marker analysis of the first population identified nominal associations of five genes with migraine. After applying a false discovery rate correction of 10%, the differences remained significant only for *DRD2* (rs2283265) and *TH* (rs2070762). Multiple-marker analysis identified a five-marker T-C-G-C-G (rs12363125-rs2283265-rs2242592-rs1554929-rs2234689) risk haplotype in *DRD2* and a two-marker A-C (rs6356-rs2070762) risk haplotype in *TH* that remained significant after correction by permutations. These results, however, were not replicated in the second independent cohort.

Conclusion: The present study does not support the involvement of the *DRD1*, *DRD2*, *DRD3*, *DRD5*, *DBH*, *COMT*, *SLC6A3* and *TH* genes in the genetic predisposition to migraine in the Spanish population.

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Migraine with aura:
Two SNPs [rs2097629 in **DBH** and rs40184 in **SLC6A3** are significant.

The present study does not support the involvement of the DRD1, DRD2, DRD3, DRD5, DBH, COMT, SLC6A3 and TH genes in the genetic predisposition to migraine.

Conclusion:

- Dopamine is possibly involved in some of the premonitory Sx of migraine, which could be treated with dopamine antagonists
- Dopamine and dopamine agonists may have a therapeutic role in headache phase of migraine, based on the recent knowledge of hypothalamic A11 nucleus.