23th南區頭痛讀書會

Migraine 100---

the most important events in the history of migraine research between 1910 and 2010

Ergotamine and migraine (~1940)

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- Isolation and clinical introduction of ergotamine

  ---*Stoll,1918*
- Further establishing the vasodilation in migraine and the constrictive action of ergotamine

  ---*Graham and Wolff, 1938*
- Pain-sensitive structures in the head (1940)

  ---*Ray and Wolff, 1940*

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Ergotamine (1918-1938)

Ergotamine

- Ergotamine:
  The most important milestones in the early 20th century.
- Chinese and Arabs:
  "*Poudre obstetricale*" (powder for delivery) before 16th century
- Edward Woakes: (1837–1912): British ENT-surgeon recommended ergot for the treatment for migraine in 1868

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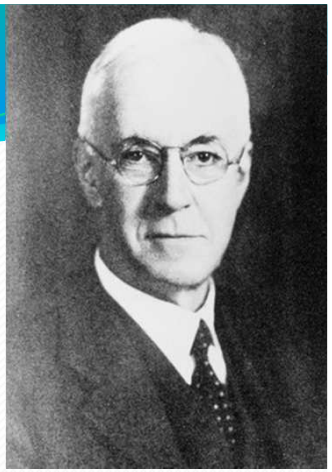
Edward Woake's report

Woakes described the fourth case as follows

Case IV. Hemicrania. *John Gray, aged about 35, has been repeatedly under treatment for that form of neuralgia known as brow ague. His attacks have been cured alike by quinine and sesquioxide of iron. Sometimes they are very severe, and the treatment long continued. He was last seen in May 1868, when he had a very sharp attack of neuralgia of the right temple. He was ordered to take, every four hours, an ounce of a mixture of two drachms of liquid extract of ergot in six ounces of infusion of ergot. After taking this for two or three days, he was cured more satisfactorily and quickly than in his former attacks* (10).

The early use of ergotamine in migraine. Edward Woakes' report of 1868, Cephalalgia 2002, 22, 686–691

Sir Henry Dale



- In 1906:
  --The liquid extract of ergot blocked the effects of stimulation of the sympathetic nerves.
  --Lower dosage: being vasocontrictive.

History of the use of ergotamine and dihydroergotamine in migraine from 1906 and onward, Cephalalgia 2008; 28:877–886

Stoll

- Ergot treatment had been unreliable because of varying alkaloid content.
- in 1918: Stoll isolated ergotamine from ergot

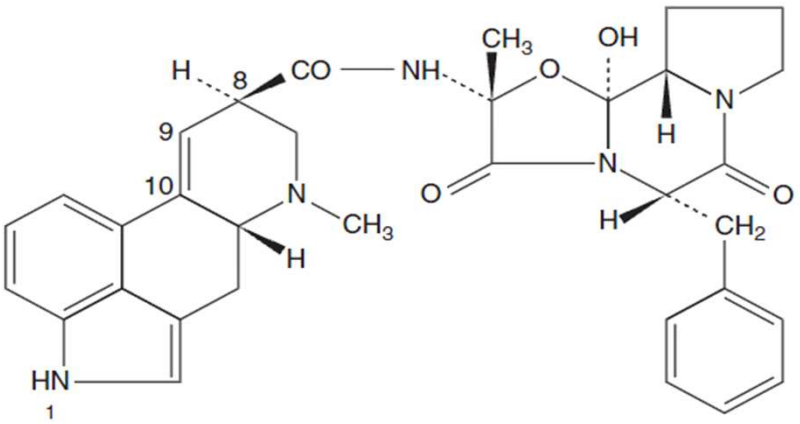


Figure 1 Chemical structure of the alkaloid ergotamine. Dihydroergotamine is hydrogenated at the double-binding 9–10.

History of the use of ergotamine and dihydroergotamine in migraine from 1906 and onward, Cephalalgia 2008; 28:877–886

Rothlin and Maier:

- Rothlin:
  --Ergotamine(adrenolytic properties) would counteract the sympathicotonic effects in migraine
  --Evidenced by a pale face in some patients
- Maier : 80 patients with “sympathicotonic conditions”

Trautmann and Tzanck

- Trautmann:
  use placebo controls to found the drug effective
- Tzanck: use ergotamine in "équivalents gastriques de la migraine" from 1860 and published data on 101 patients 3 years later

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in the USA

- Ergotamine was introduced in the USA
- In 1934, several reports use in migraine

--Lennox:
40/45 patients--relief after injections of ergotamine

--Logan and Allen: effective in 67/71 attacks in 9 patients

- In 1935, Lennox and Von Storch
efficacious in 90% of 109 patients treated with intravenous ergotamine

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- At beginning:
  1. Blood pressure changes
  2. Uterine contractions

  Nearly 1 hour:
  1. Relief of headache
  2. Time-effect curve for the effect on arteries

Vasodilation in migraine; constrictive action of ergotamine

Graham and Wolff (1938)

- Ergotamine: decreased migraine headache
  --the pulse amplitude measured over the temporal artery.
- Migraine: a condition with initial cerebral vasoconstriction followed by extracranial reactive vasodilation.

History of the use of ergotamine and dihydroergotamine in migraine from 1906 and onward, Cephalalgia 2008; 28:877–886

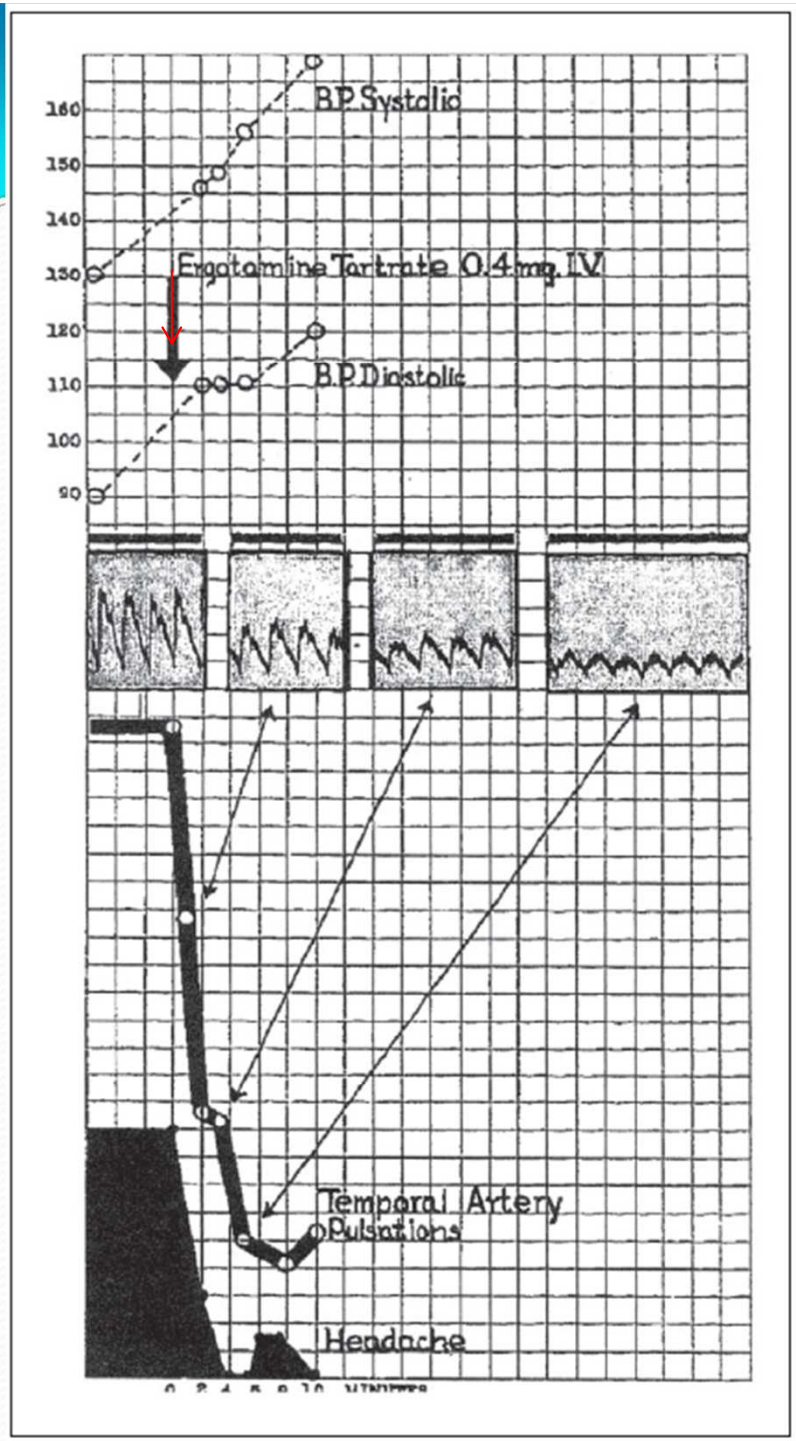

Fig 1.—One of the famous pictures from the paper by Graham and Wolff, 1938. Relation between pulsation amplitude of the temporal artery and the headache intensity following the administration of ergotamine tartrate. Representative records of the photographic record are inserted. The initial temporal artery amplitude was taken as 99%.[7]

Graham and Wolff

- Ergotamine injections
  →1. amplitude of pulsations of external carotid vessel
  2.intracranial vessel (indirectly):
  CSF pulsation in the lumbar subarachnoid space
- Decrease in amplitude, decline of headache intensity,
  →Vascular hypothesis
  the most important figures in migraine research of the 20th century

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- “the most acceptable explanation of the headache-ending effect:
  --cranial arterial walls which are painfully stretched and dilated
  --Narrow through the vasoconstrictor action of ergot”
- For many years, ergotamine and its derivative dihydroergotamine(DHE) were the only specific antimigraine drugs.

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- A more recent European consensus found it the drug of choice in a limited number of migraine sufferers who have infrequent or long duration headaches.

Pain-Sensitive Structures in the Head (1940)

Ray and Wolff

Pain-Sensitive Structures

- Ancient texts on headache, Van Beverwijck's *Treasure of Unhealthiness of 1642.*
- Ray and Wolff : 1930s

--" Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache." *Archives of Surgery.* 1940;41:813-856.

--Great importance: a mainstay of migraine literature

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Ray and Wolff --Method

- Surgical exposure of structures within and outside the cranium
- Cooperative and intelligent, not only pain reported but describe its site and nature.
- Free of apprehension with pain, so that a minimal amount of local analgesia was required.
- Not too inarticulate to describe their sensation.
- The structures were free of disease process.
- The observations were recorded in detail(localization, what kind of stimulation) in operating room.

Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Archives of Surgery. 1940;41:813-856

Ray and Wolff --Observations

30 patients with local anesthesia:

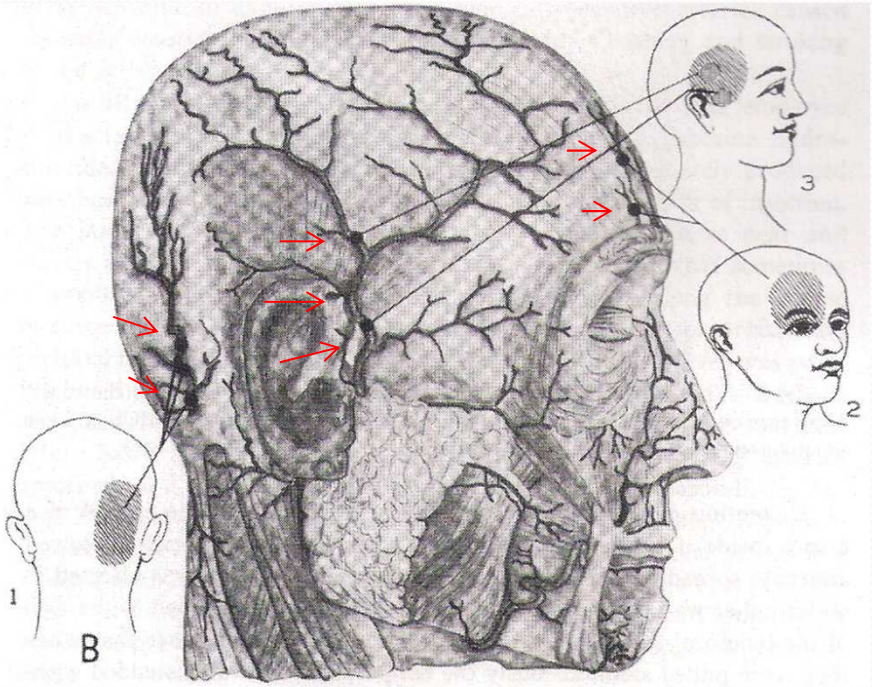
- Extra- and intracranial structures:

  --Scalp, galea, fascia, muscles, arteries, veins, sinuses

Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Archives of Surgery. 1940;41:813-856

Ray and Wolff --Observations

- Scalp, galea (epicranial aponeurosis), fascia, muscles:
  --150 observations, 30 subjects
  --thermal,chemical, mechanical, electrical stimulation



Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Archives of Surgery. 1940;41:813-856

- Dural artery (middle meningeal artery):
  --96 observations, 11 subjects
  --stimuli: faradizing, distending, stroking, stretching, crushing

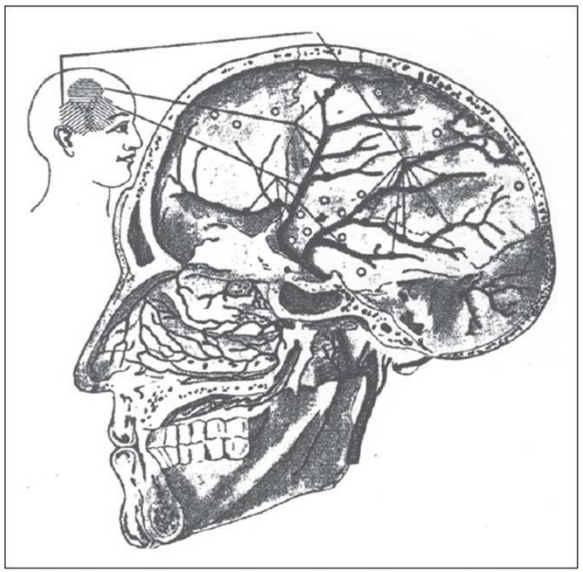
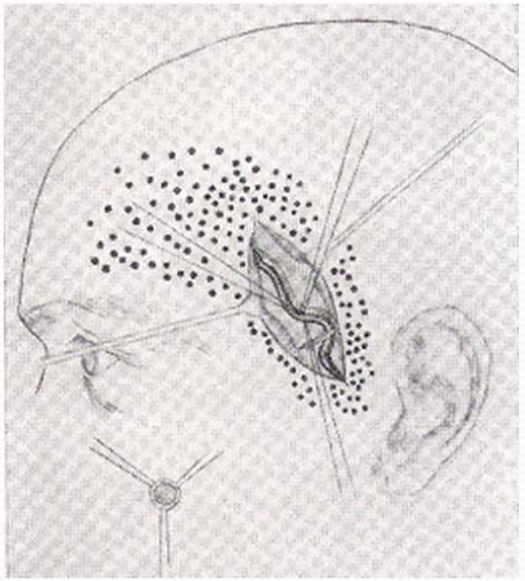
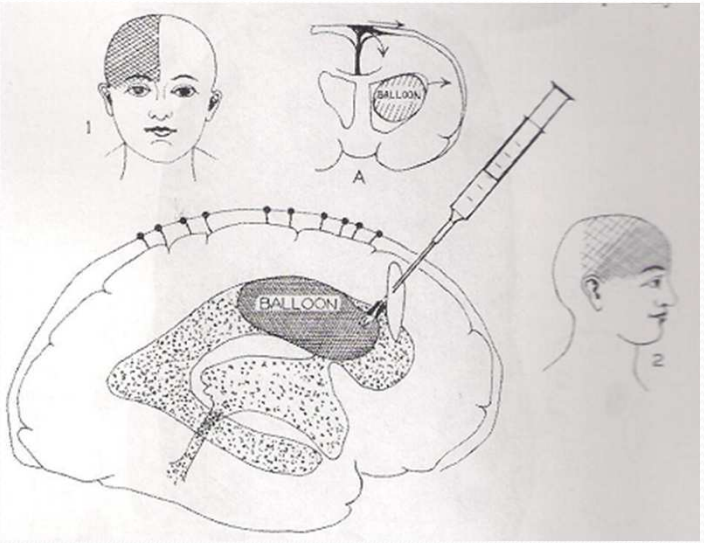


Fig 2.—One of the many figures from the paper by Ray and Wolff. Stimulation of the middle menigeal artery caused pain in the ipsilateral temporal region.[8]



Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Archives of Surgery. 1940;41:813-856

- Ventricles, aqueduct of Sylvius, Choroid plexuses
  --24 observations, 4 subjects
  --a balloon placed through a small opening into anterior horn and body of lateral ventricle



Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Archives of Surgery. 1940;41:813-856

Ray and Wolff --Conclusions

- Pain-sensitive structure

--Extracranial: most tissues, arteries in particular

--Intracranial:

Venous sinuses, venous tributaries from the surface of the brain, parts of the dura at the skull base, dural arteries, cerebral arteries at the base

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Ray and Wolff --Conclusions

- *Not* sensitive to pain:

--skull, brain parenchyma, most of the dura, pia-arachnoid, ependymal lining of the ventricles, choroid plexuses

Experimental studies on headache. Pain-sensitive structures of the head and their significance in headache. Archives of Surgery. 1940;41:813-856

- Stimulation of the pain-sensitive structures on or above the tentorium cerebelli:
  1. Pain in front of a line drawn vertically from the ears across the top of the head.
  2. Pathways: trigeminal nerve
- Stimulation on or below the inferior the tentorium:
  1. Pain in behind this line
  2. Pathway: glossopharyngeal, vagus nerve, 3 upper cervical roots.

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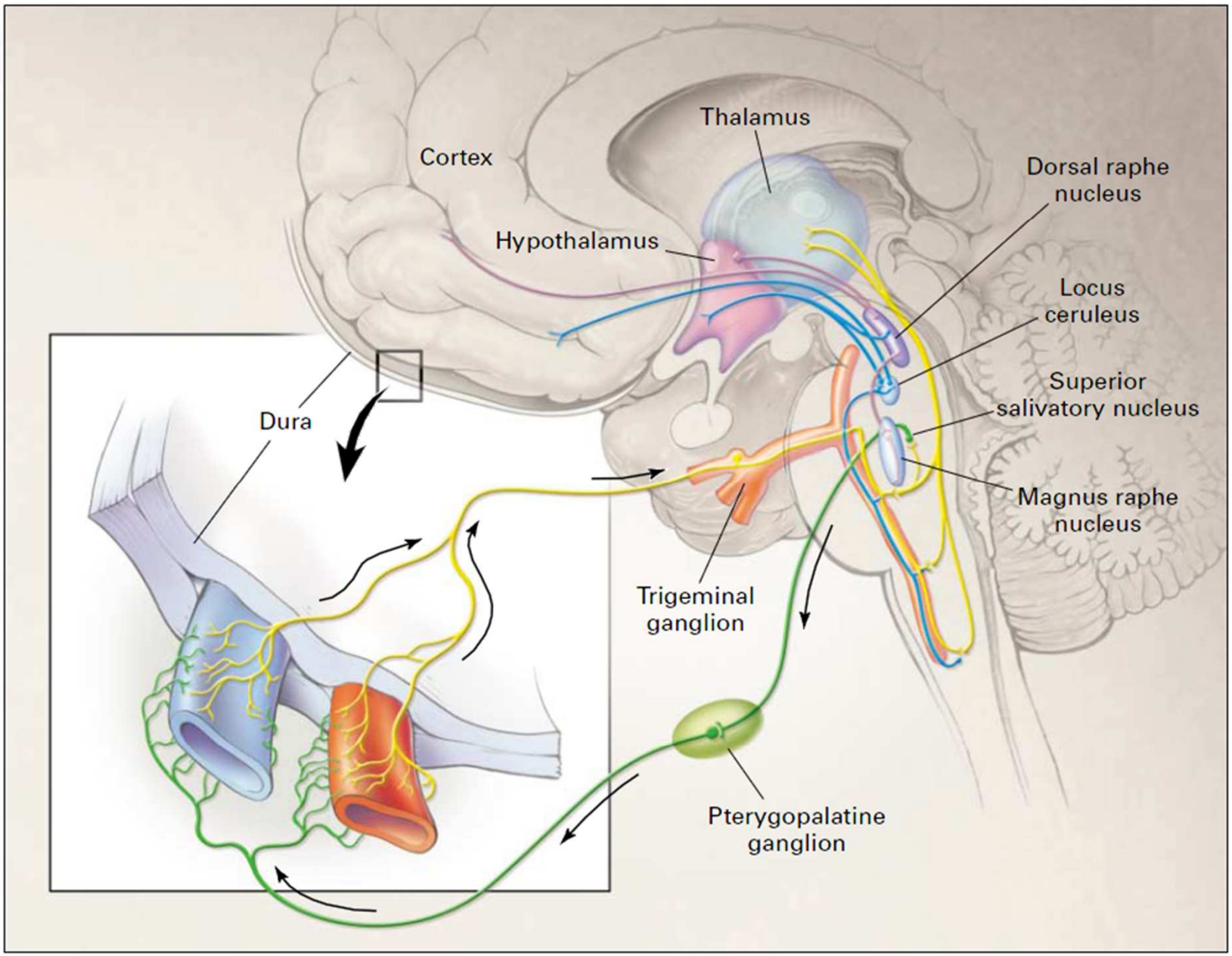

Figure 1. Pathophysiology of Migraine.

Ray and Wolff

- *Not* painful

--Focal and short-lasting stimulation of dura mater/ a small blood vessel in the pia mater

- Painful

--Long lasting stimulation and/or stimulation of a large area of the dura mater or the pia
(1)meningitis (2)subarachnoid hemorrhage.

-- spatial and temporal summations

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