



Neurophysiological Rationale for Cannabinoids in Fibromyalgia

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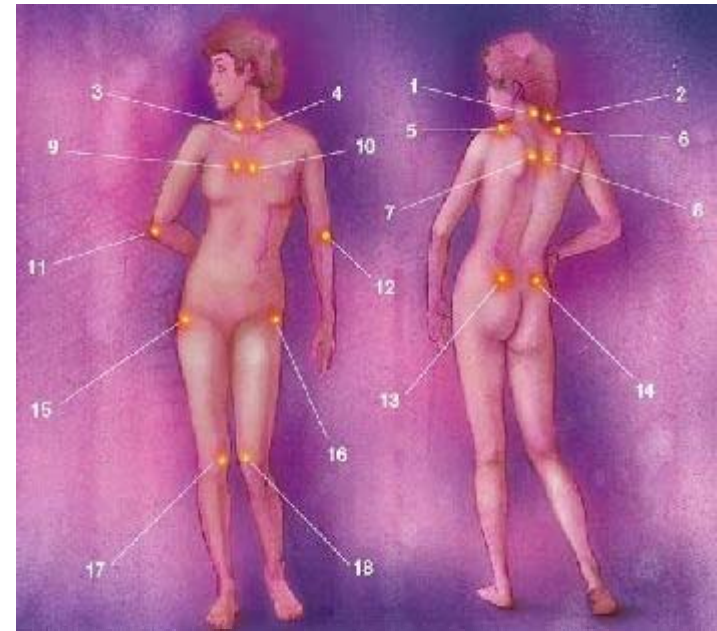
Disclosure of information

- This study was made possible by an unrestricted grant provided by Valeant Canada Limited.



What is fibromyalgia?

- Established in 1990 by the American College of Rheumatology: Fibromyalgia (FM) includes a widespread pain for at least 3 months and point tenderness with 4kg of pressure at 11 or more of 18 characteristic tender points.





What more?

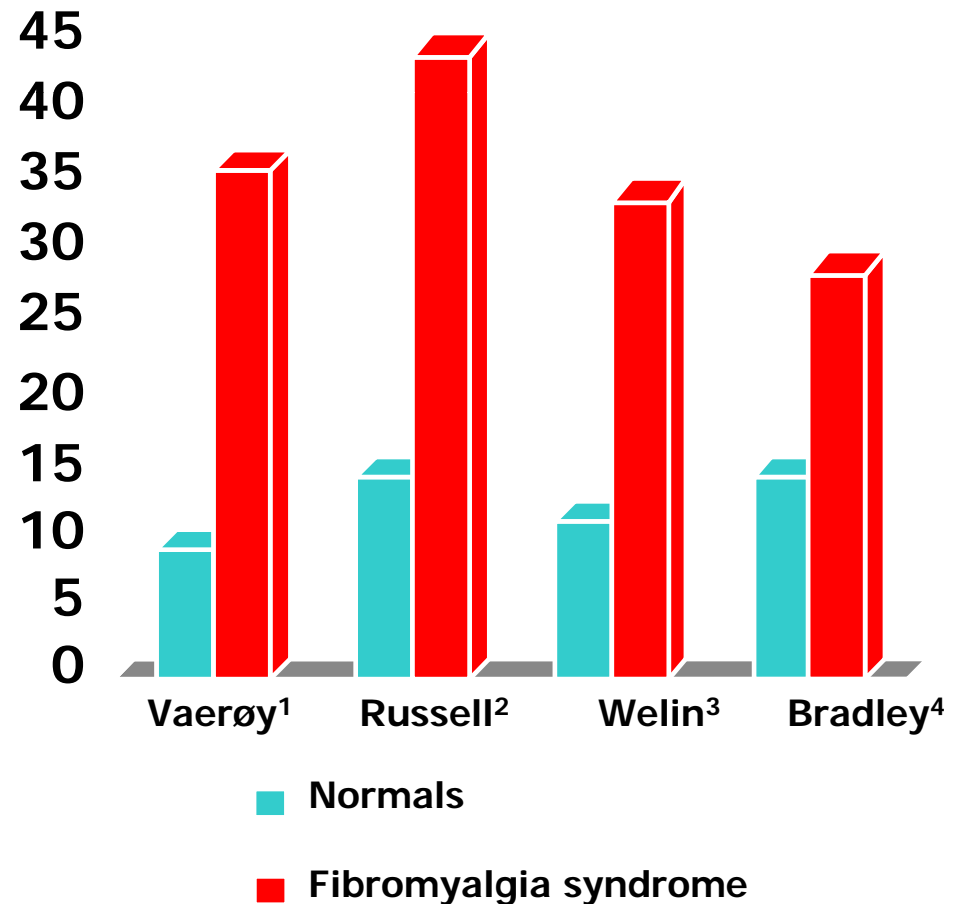
- Sex differences.
- Lack of consistent tissue abnormalities but presence of hyperalgesia and allodynia (peripheral sensitization).
- Central sensitization (neuroplasticity).
- Immune activation.
- Abnormal glial cell activation.
- Abnormal temporal summation of pain. (DNIC)
- Loss of endogenous pain control mechanisms. (windup)
- Depression.
- Insomnia.
- Loss of appetite.

Where to start?

There is a strong correlation between the increase of Substance P (SP) in the cerebrospinal fluid (CSF) of FM patients, and higher pain scores. (Russell et al., 94, Welin et al, 95)

- There is also a correlation possible between high SP in the CSF and low levels of serotonin and its precursor, tryptophan, in FM patients' serum resulting in higher pain scores and severe sleep disturbances. (Murphy et al., 87, Schwarz et al., 99)

Fibromyalgia Cerebrospinal
Fluid Substance P

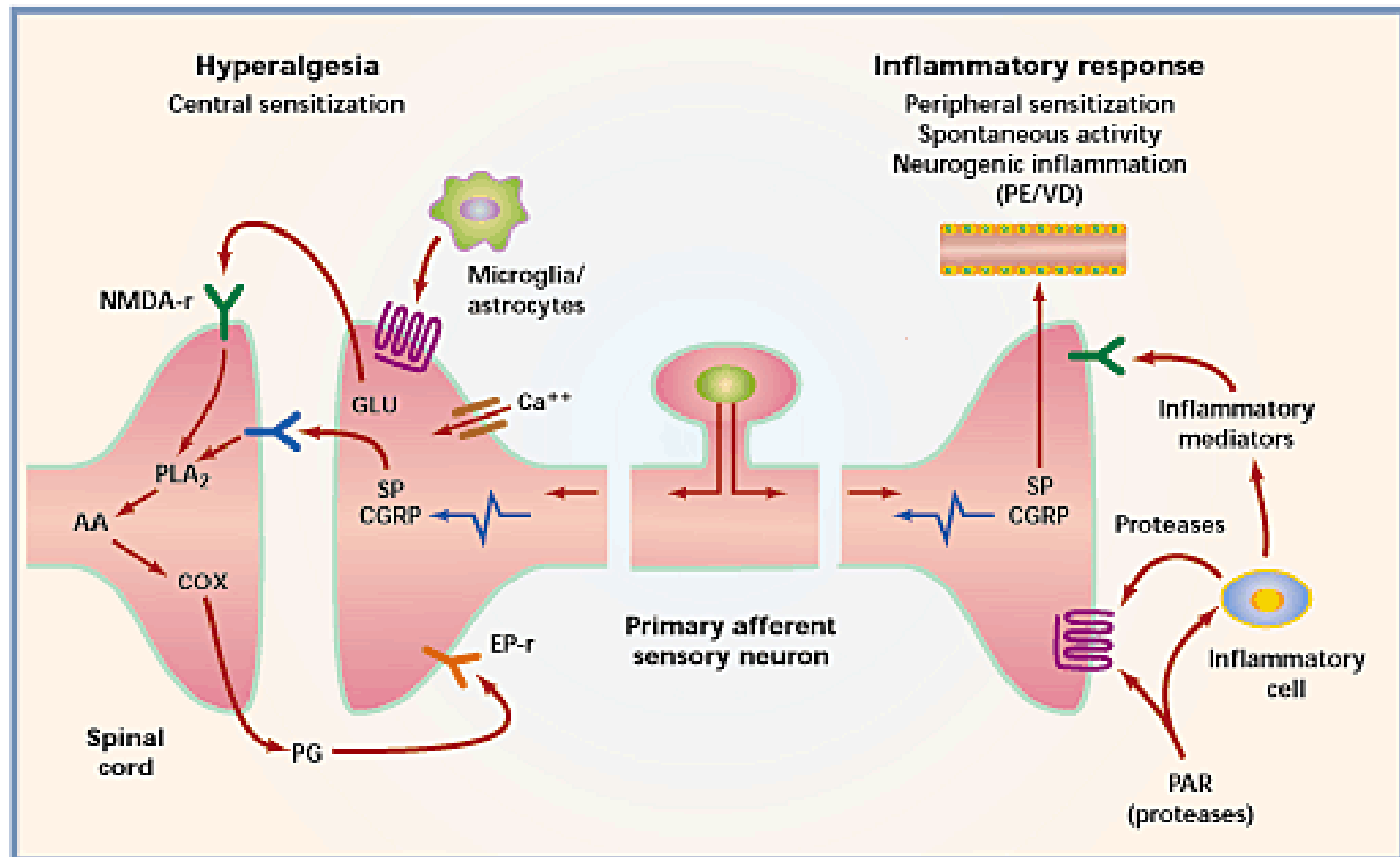




Reasons for SP elevation

- Primary FM: An increase in Nerve growth factor (NGF) in unmyelinated interneurons seems to be the cause.
- Secondary FM: The inflammation is caused by a rheumatic or infectious disorder.

Central vs Peripheral sensitization

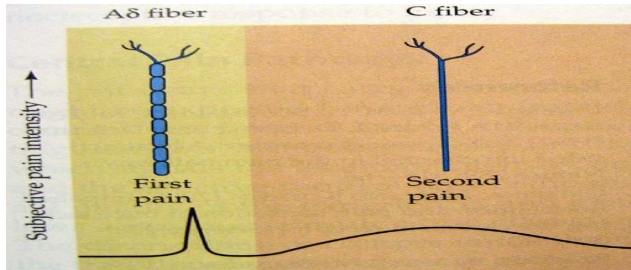




Central sensitization in FM

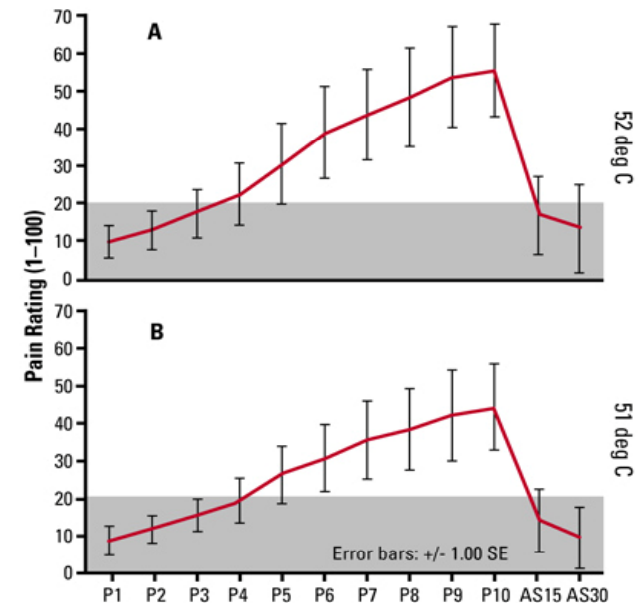
- Immediate Central sensitization:
 - - Via NMDA and NK1 receptors.
- Functional changes in the central nervous system (neuroplasticity).
- Delayed central sensitization:
 - - Increased excitability of spinal cord neurons.
 - - Enlargement of their receptive fields.
 - - Reduction in pain threshold.
 - - Recruitment of novel afferent inputs.

Windup abnormalities



- Pain perception during windup is higher in FM patients.
- Windup-induced aftersensations are also higher and last longer in FM patients.

FIGURE
Mean (\pm SD) Windup Ratings of Ten Normal Study Participants



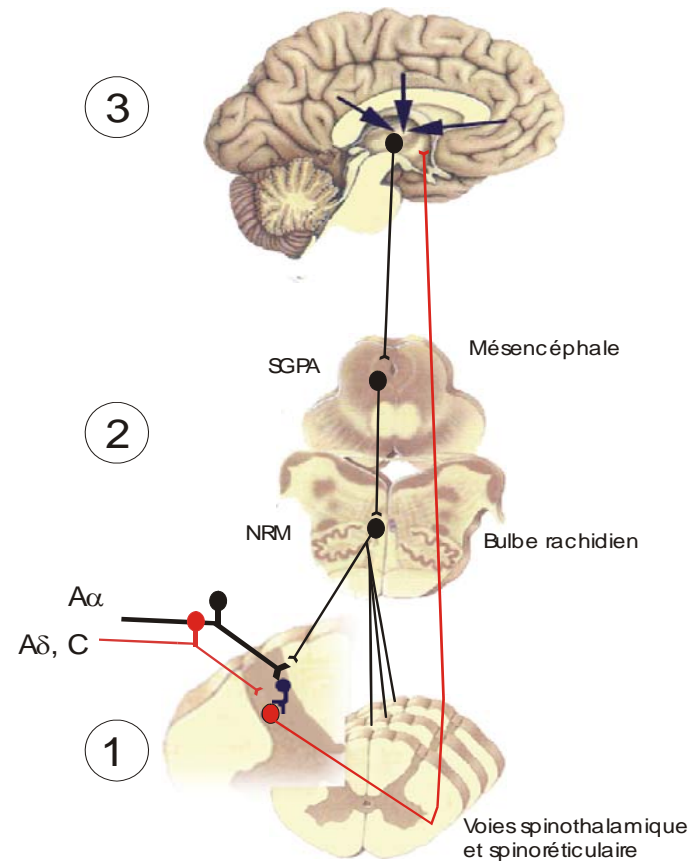
The subjects received either 10 repetitive 52 °C (A) or 51 °C (B) heat pulses (P) to the hands at 0.33 Hz. Mixed model ANOVAs showed a significant increase of pain ratings from first (P1) to tenth heat pulse (P10) ($P < .001$). There was a significant pulse x temperature interaction noted ($P < .005$), indicating that increasing stimulus temperatures resulted in augmented WU. WU aftersensations rapidly decayed below painful levels 15 seconds after the last pulse in all participants. A numerical pain scale was used (0–100). The shaded areas represent pain ratings below threshold. AS15, aftersensation 15 seconds; AS30, aftersensation 30 seconds.

SD=standard deviation; ANOVA=analysis of variance; WU=windup.

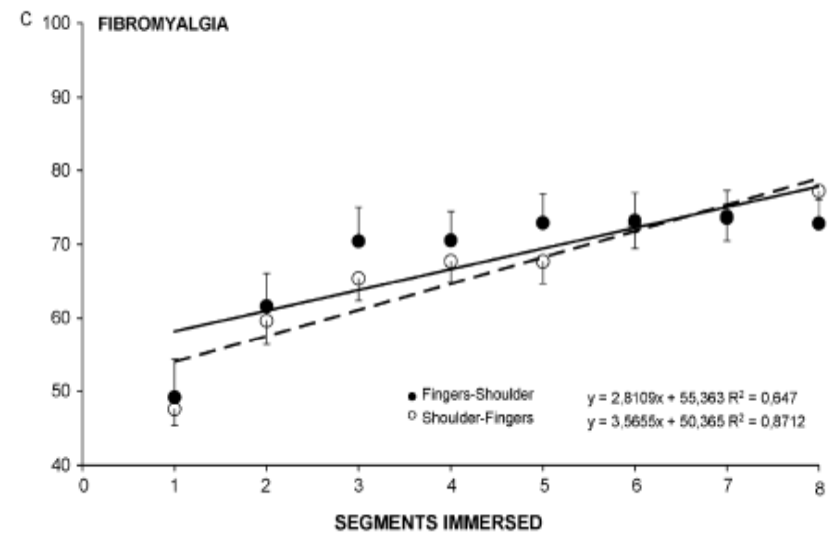
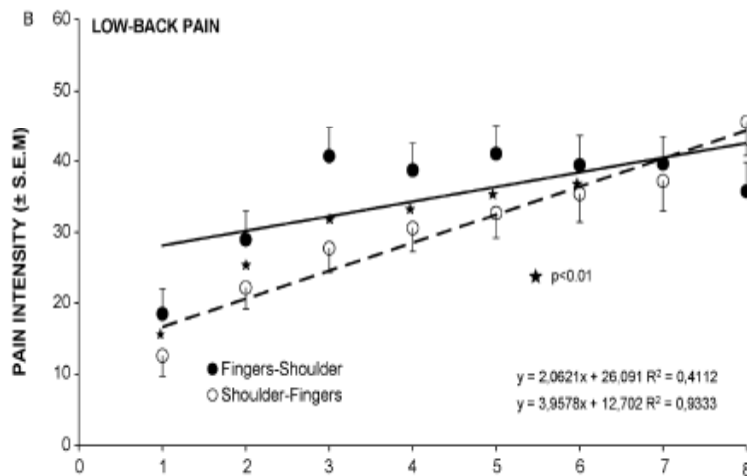
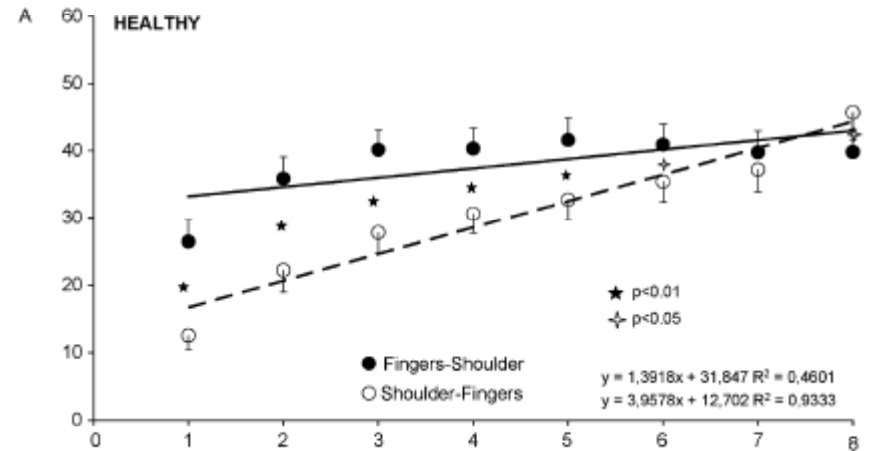
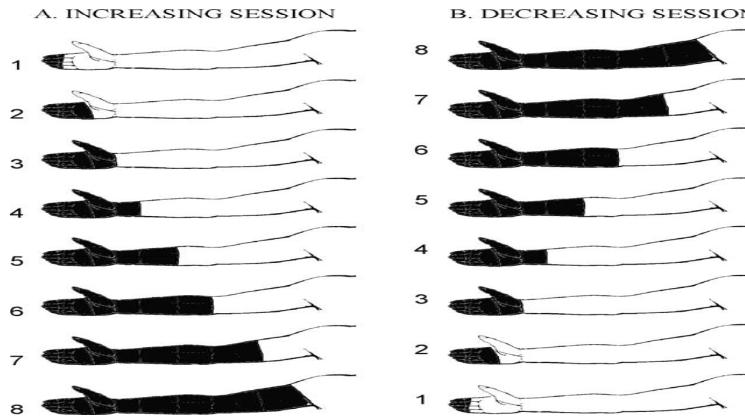
Staud R, Spaeth M. *CNS Spectr*. Vol 13, No 3 (Suppl 5). 2008.


Endogenous mechanisms of pain control

- Diffuse noxious inhibitory control: descending opioid mechanism.
- Modulated by time and surface exposure.



Dysfunctional pain control mechanisms





Role of glial cells in Central Sensitization

- Following central sensitization, there is growing evidence of an activation of spinal glial cells protecting the dorsal horn neurons, contributing to the already present hyperalgesia and the immune activation of the spinal chord (release of SP, excitatory amino acids, nitric oxide and prostaglandins).

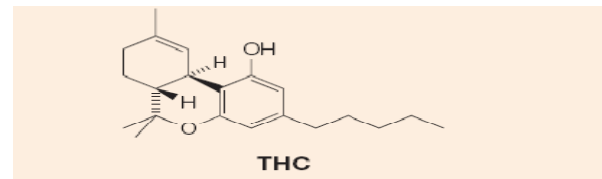
Cannabis Sativa

- Used in medicine for more than 4000 years.
- Therapeutic potential widely debated.
- Possible analgesic.
- Contains more than 60 cannabinoids.

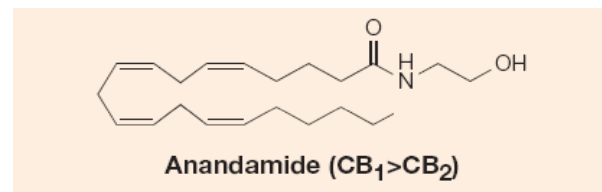


Different cannabinoids

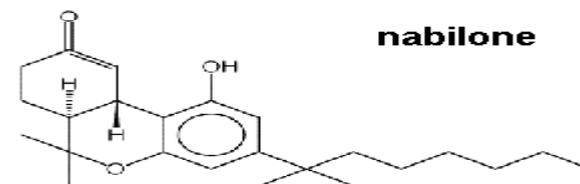
- Δ^9 -tetrahydrocannabinol
-principal cannabinoid found in cannabis sativa



- Anandamide
-Principal endogenous cannabinoid

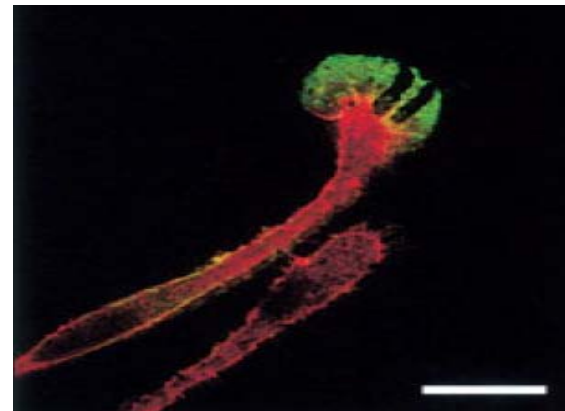
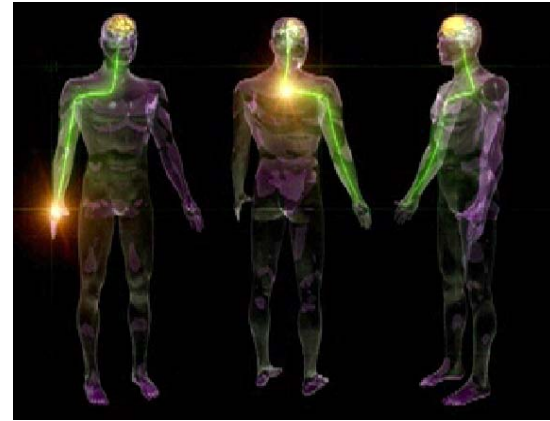


- Nabilone
-Synthetic analog of THC

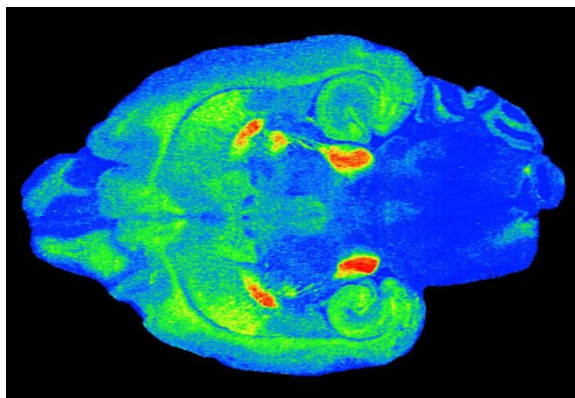
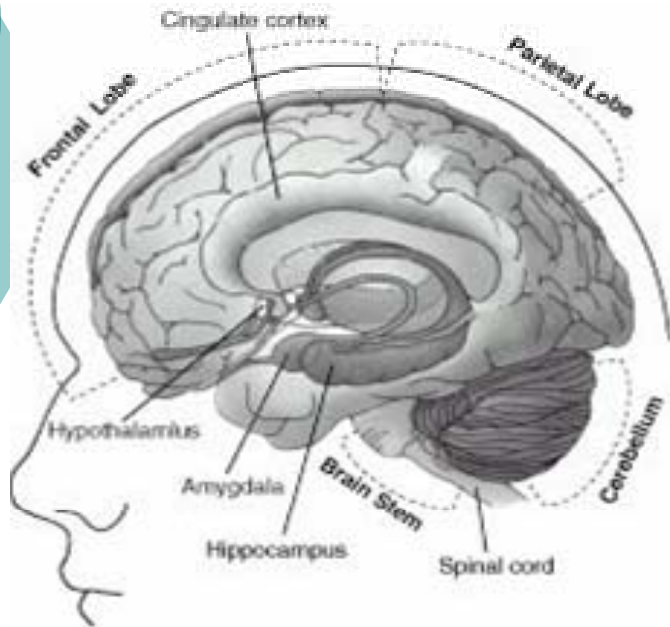


Receptors

- CB1: Found at every level of the nervous system.
- CB2: Found principally in the immune system and glial cells.



CB1 receptors and the brain



Brain Region

Functions Associated with Region

Brain regions in which cannabinoid receptors are abundant

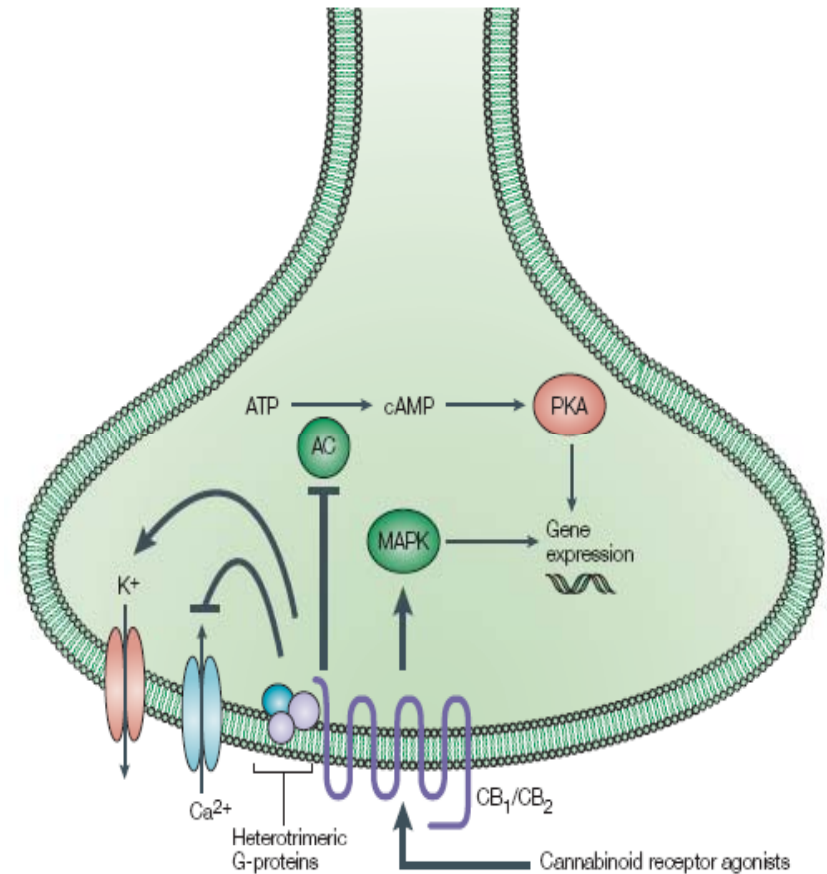
Basal ganglia.....	Movement control
Substantia nigra pars reticulata	
Entopeduncular nucleus	
Globus pallidus	
Putamen	
Cerebellum.....	Body movement coordination
Hippocampus.....	Learning and memory, stress
Cerebral cortex, especially cingulate, frontal, and parietal.....	Higher cognitive functions
Nucleus accumbens.....	Reward center

Brain regions in which cannabinoid brain receptors are moderately concentrated

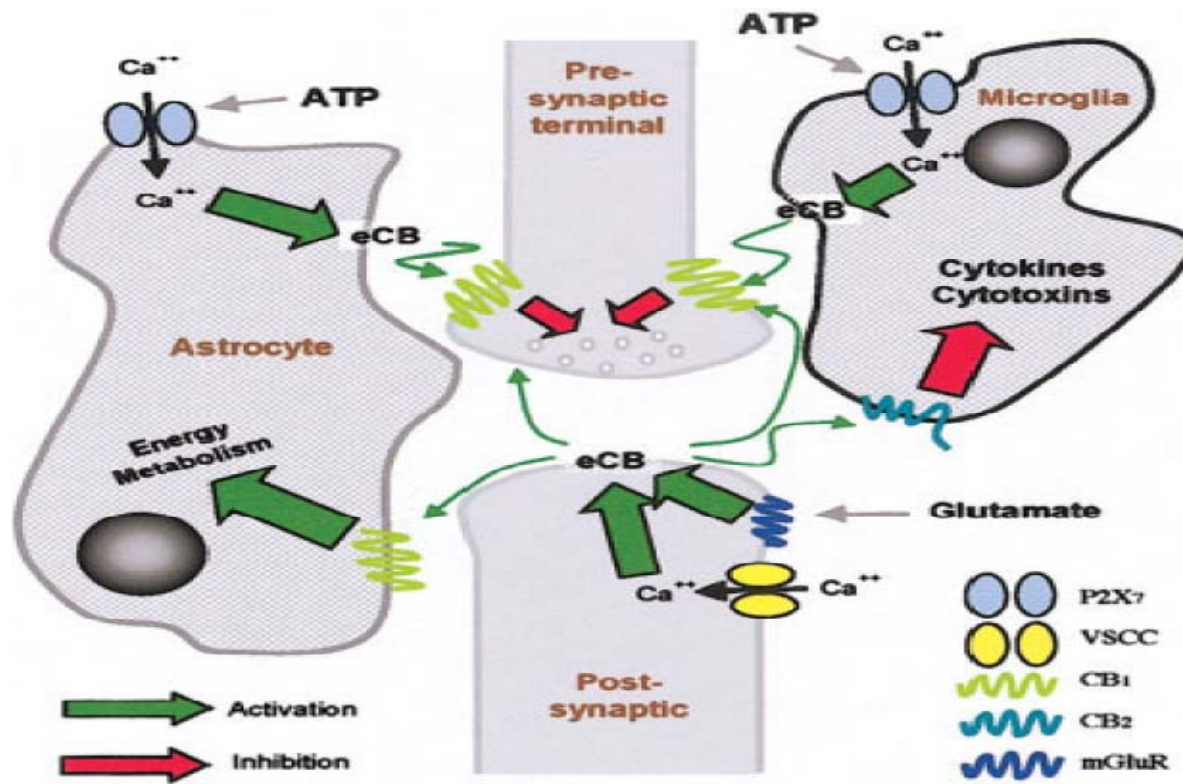
Hypothalamus.....	Body housekeeping functions (body temperature regulation, salt and water balance, reproductive function)
Amygdala.....	Emotional response, fear
Spinal cord.....	Peripheral sensation, including pain
Brain stem.....	Sleep and arousal, temperature regulation, motor control
Central gray.....	Analgesia
Nucleus of the solitary tract.....	Visceral sensation, nausea and vomiting

Mechanism of action

- Stimulation of $G_{i/o}$ heterotrimeric protein.
- Inhibition of AC » inactivation of the phosphorylation of PKA pathway.
- Stimulation of MAPK.
- Gene expression.
- Blockade of Ca^{2+} voltage-dependant canals.
- Stimulation of K^+ canals.
- Inhibition of the release of neurotransmitters.



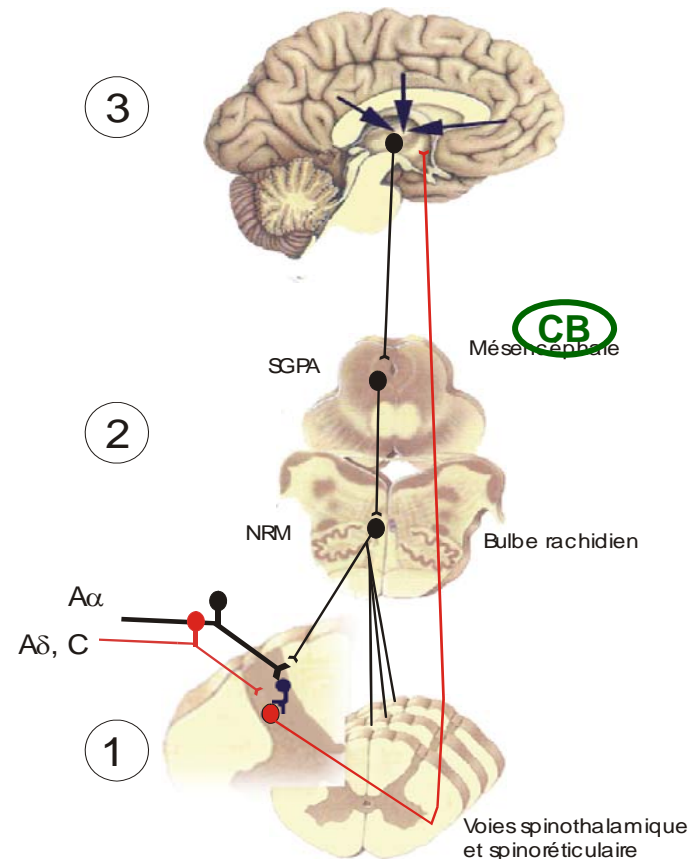
Mechanism of action (2)



Endogenous mechanisms of pain control



- Diffuse noxious inhibitory control: descending opioid mechanism.
- Implication of anandamide?
- Synergistic effect with opioids?



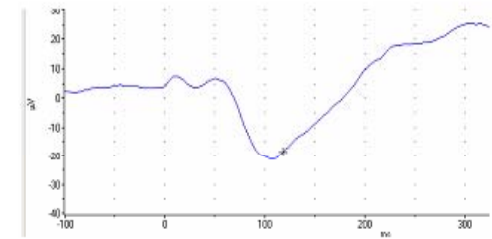
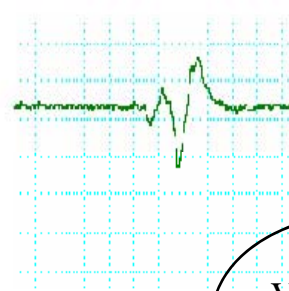
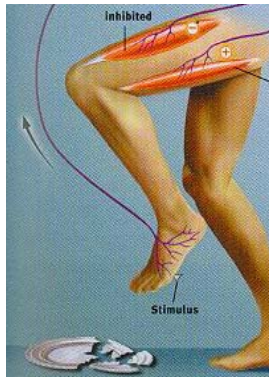
Walker et al., 1999 Roberts et al., 2005



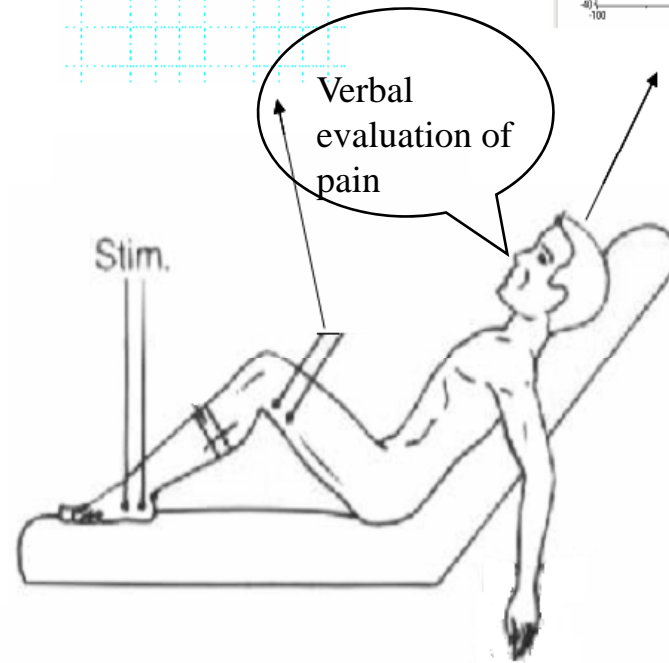
Cannabinoids and pain

- Evidence of analgesia in vivo. Eisenhac et al., 2007, Gertskeya et al., 2006, Mokha et al, 2007
- Evidence of analgesia in clinical trials for chronic pain, multiple sclerosis and cancer-related. Einharson et al., 2007, Hohmann et al., 2006, Masiono et al., 2006
- "Nabilone may be a useful addition to pain management and should be further evaluated in randomized controlled trials." Ware MA et al., 2006.
- "In general, the results of the very few well-conducted clinical trials often diverge from the highly interesting and promising findings of preclinical studies." Rammes G et al., 2005

First test: nociceptive reflexes and evoked potentials.



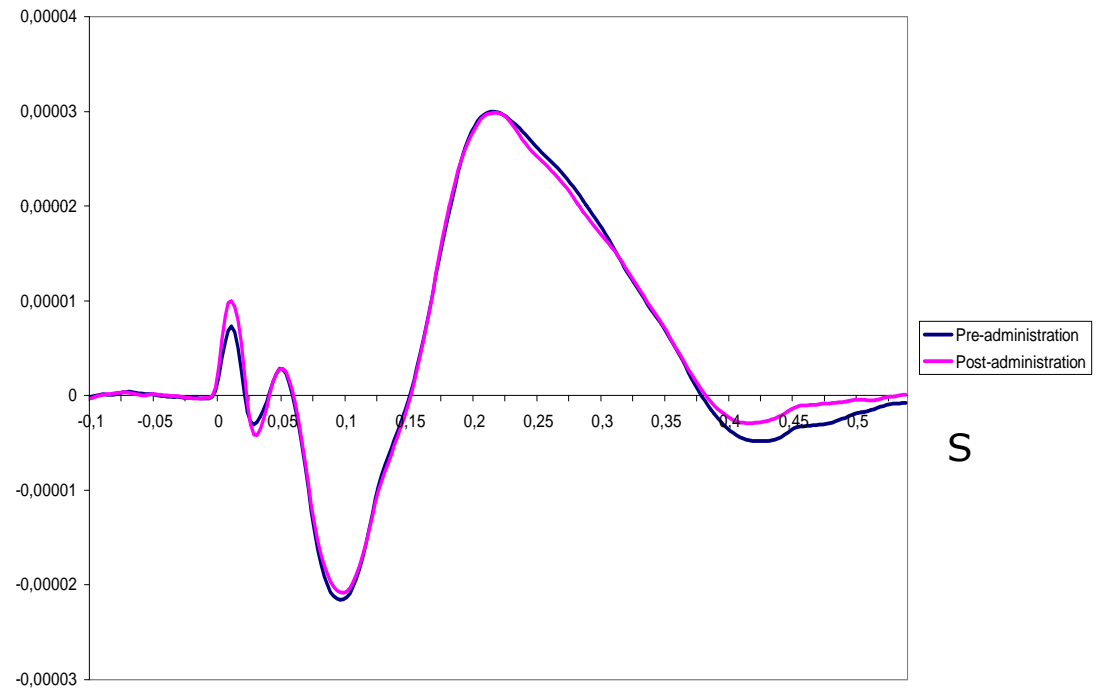
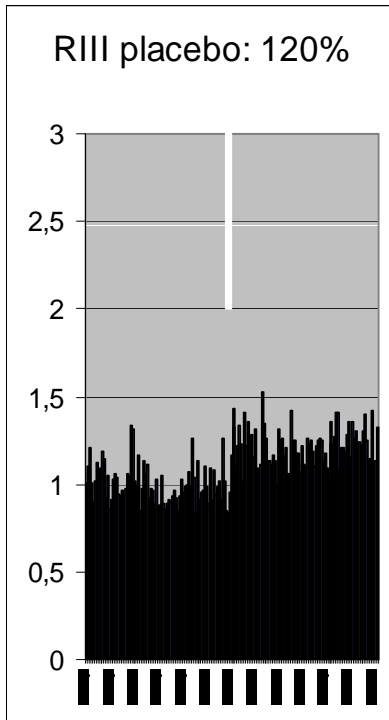
- 10 minutes of stimulation of the sural nerve at every 7 seconds.



Placebo



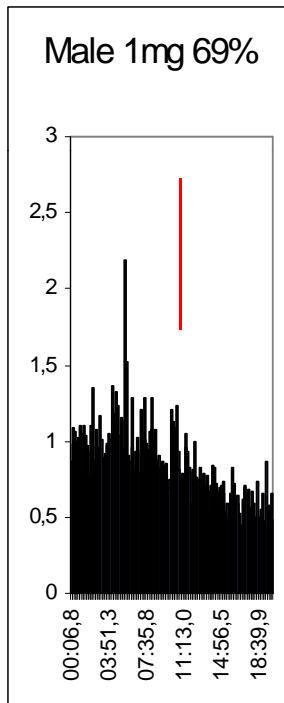
n=19



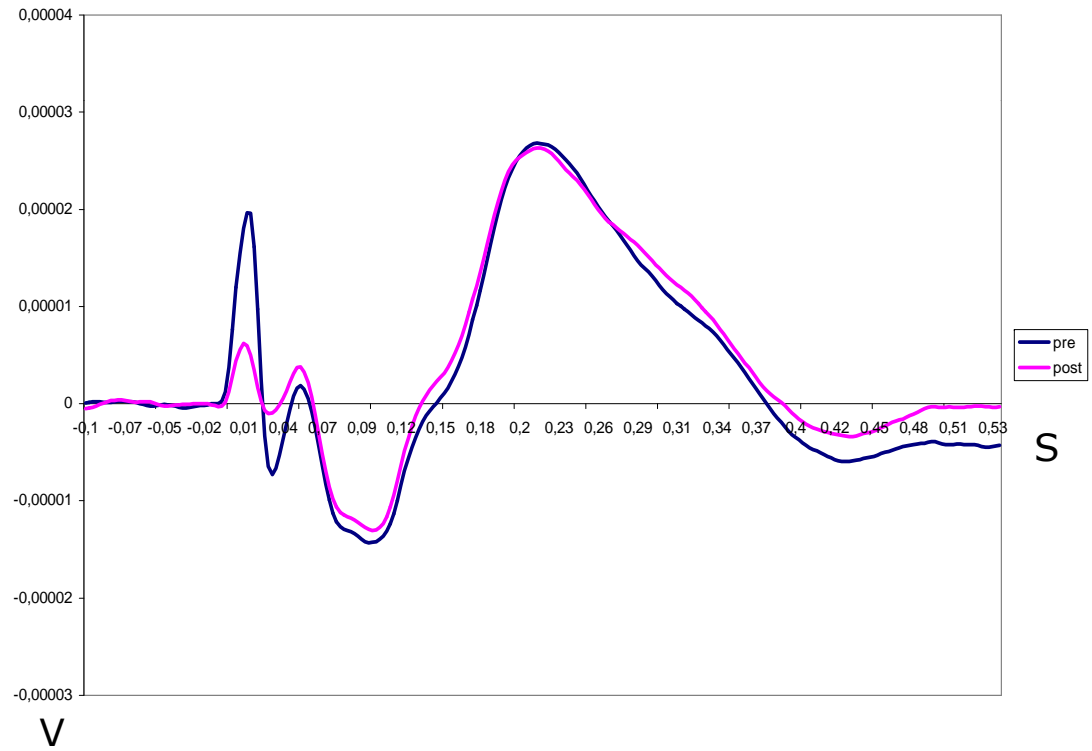
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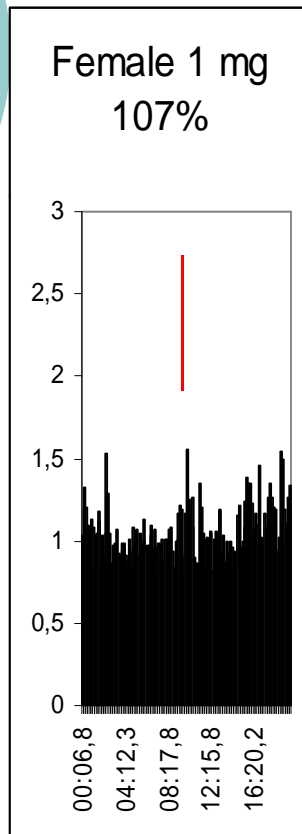
Men, 1 mg



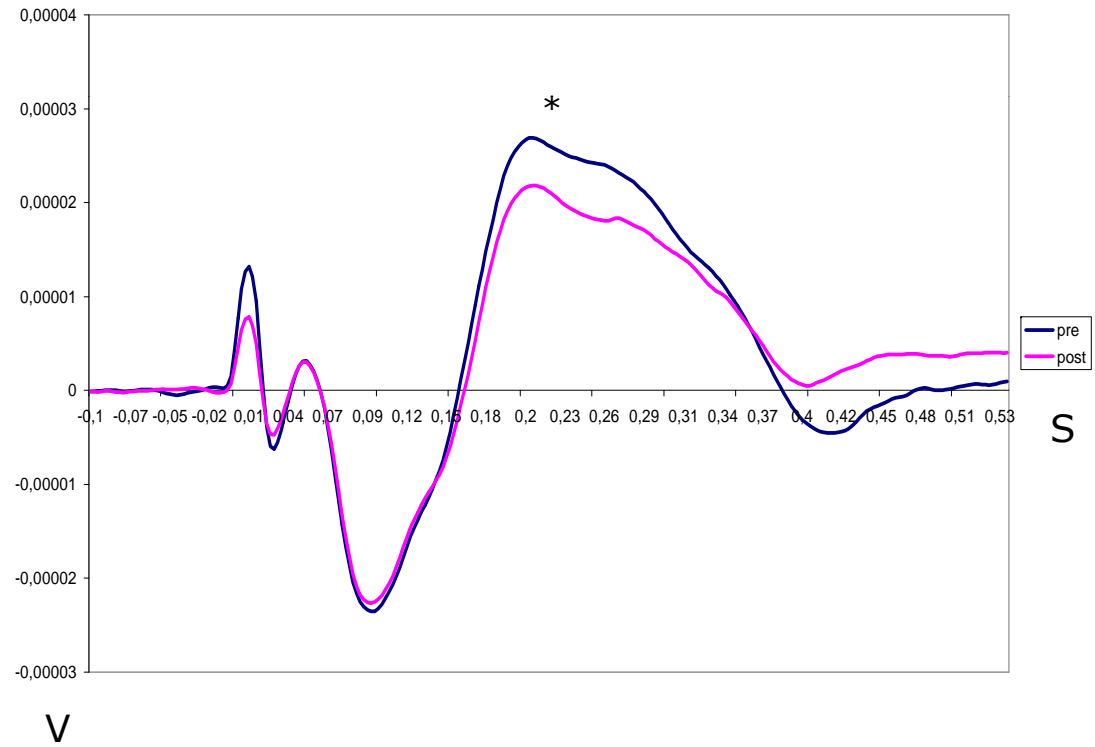
n=10



Women, 1mg



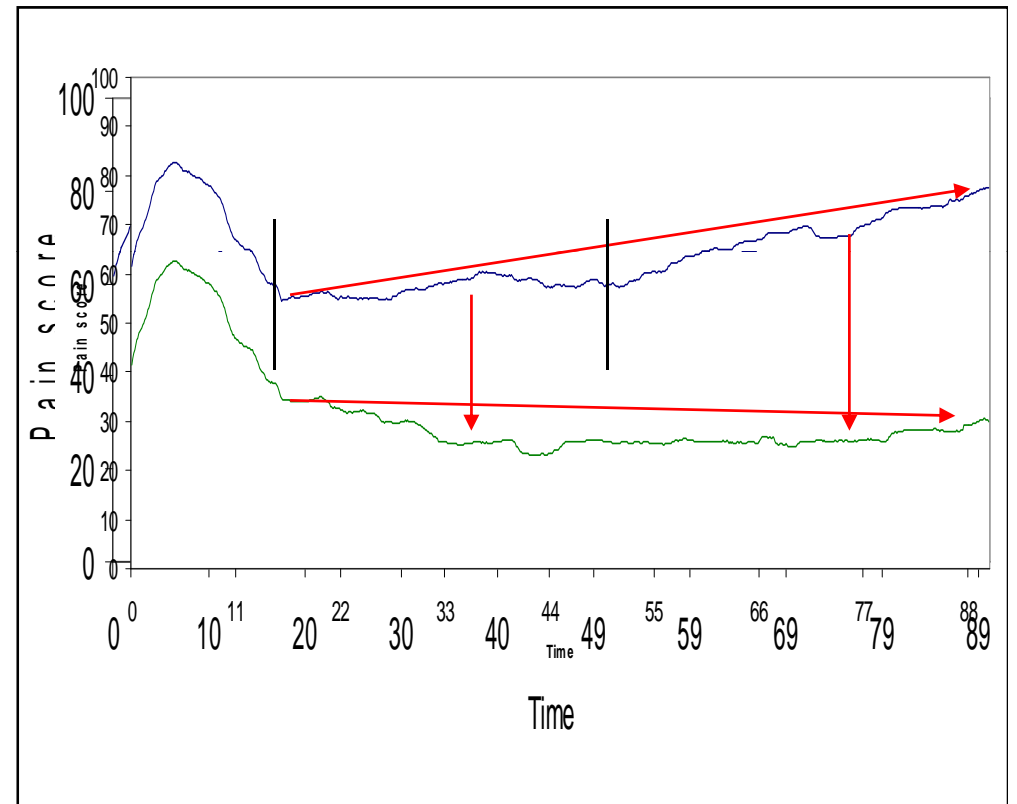
n=9





Second test: temporal summation (windup)

- Constant heat pain stimulation for 90 seconds.
- Global analgesic effect.
- Effect on windup.



Effect of nabilone on windup and DNIC



Effet du CIDN

Nabilone intake and 2 hours waiting period.

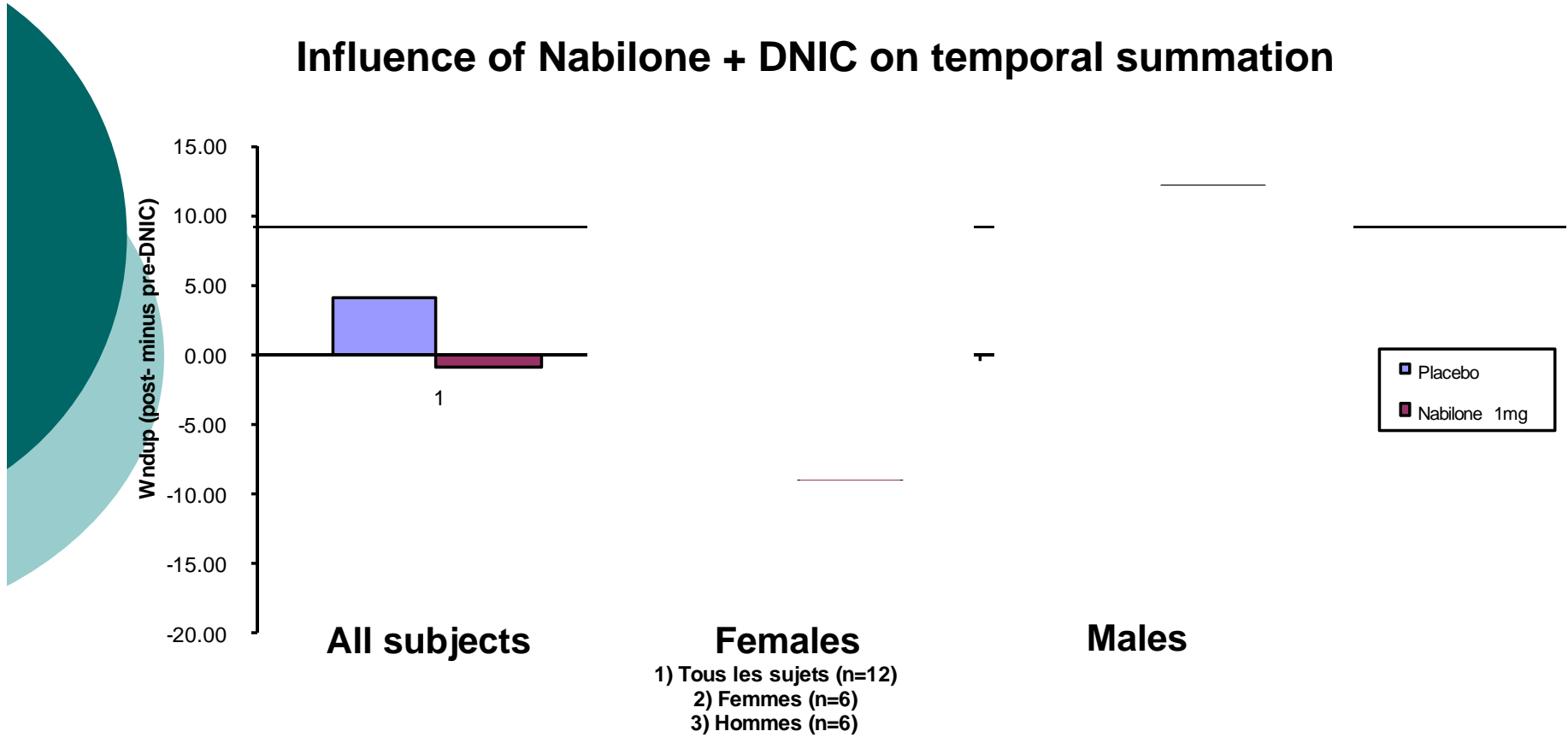


Effet du
Nabilone

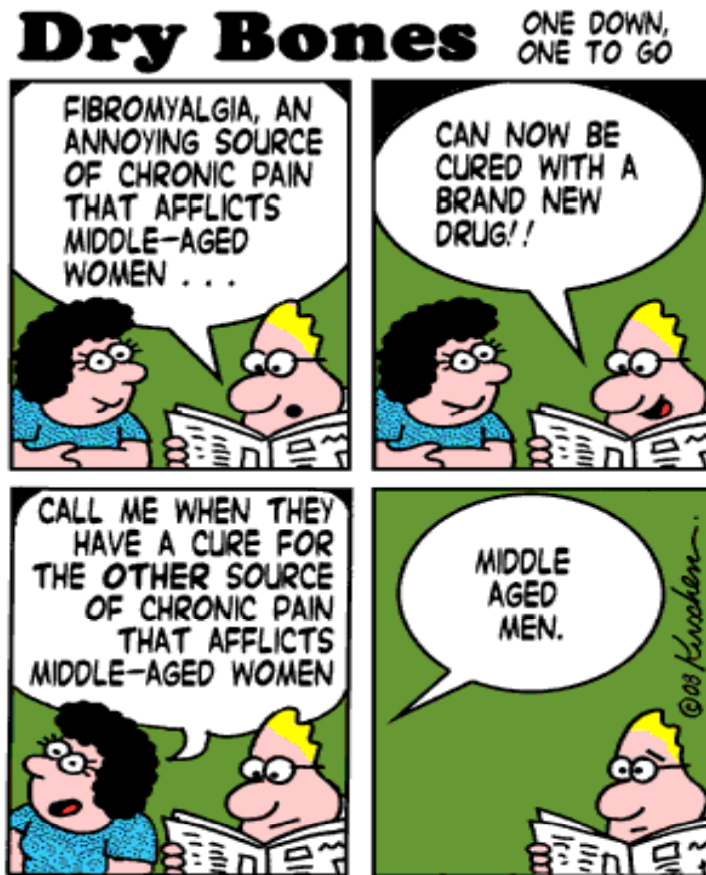


Effet du
Nabilone +
CIDN

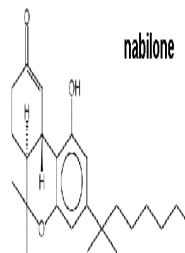
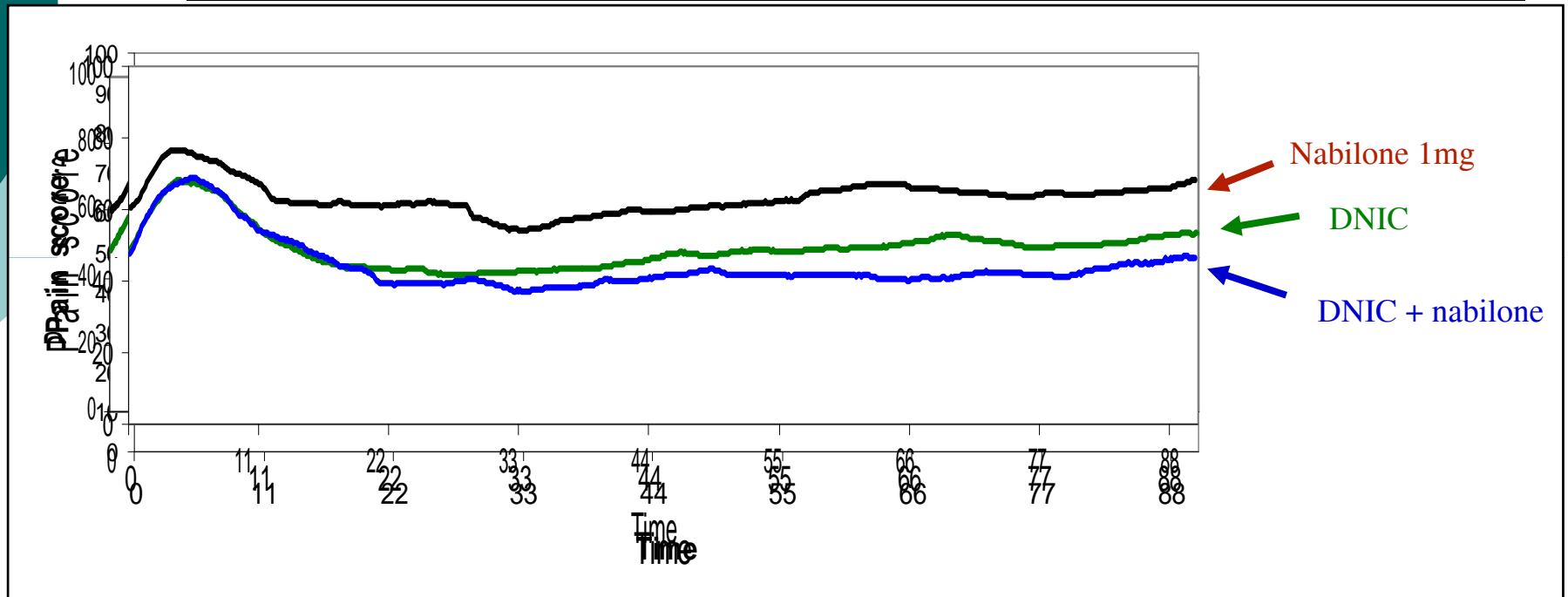
Influence of Nabilone + DNIC on temporal summation



Questions?

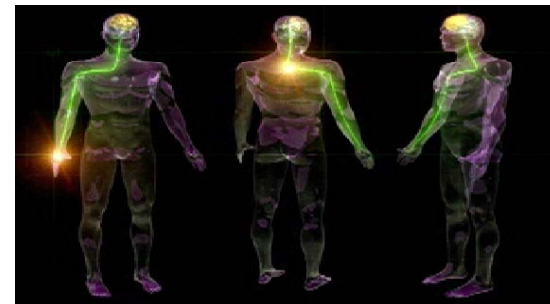
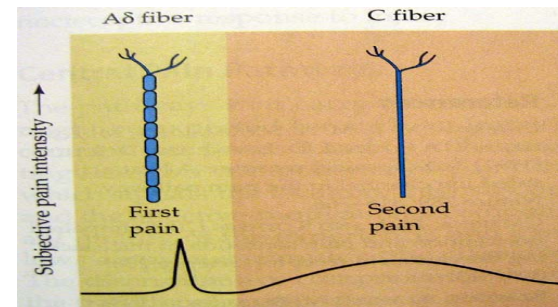


Temporal summation test, nabilone 1mg, n=12



Points à évaluer

- Effet sur les fibres A δ et C.
- Effet au niveau spinal et supra-spinal.
- Synergie possible avec opiacés endogènes.





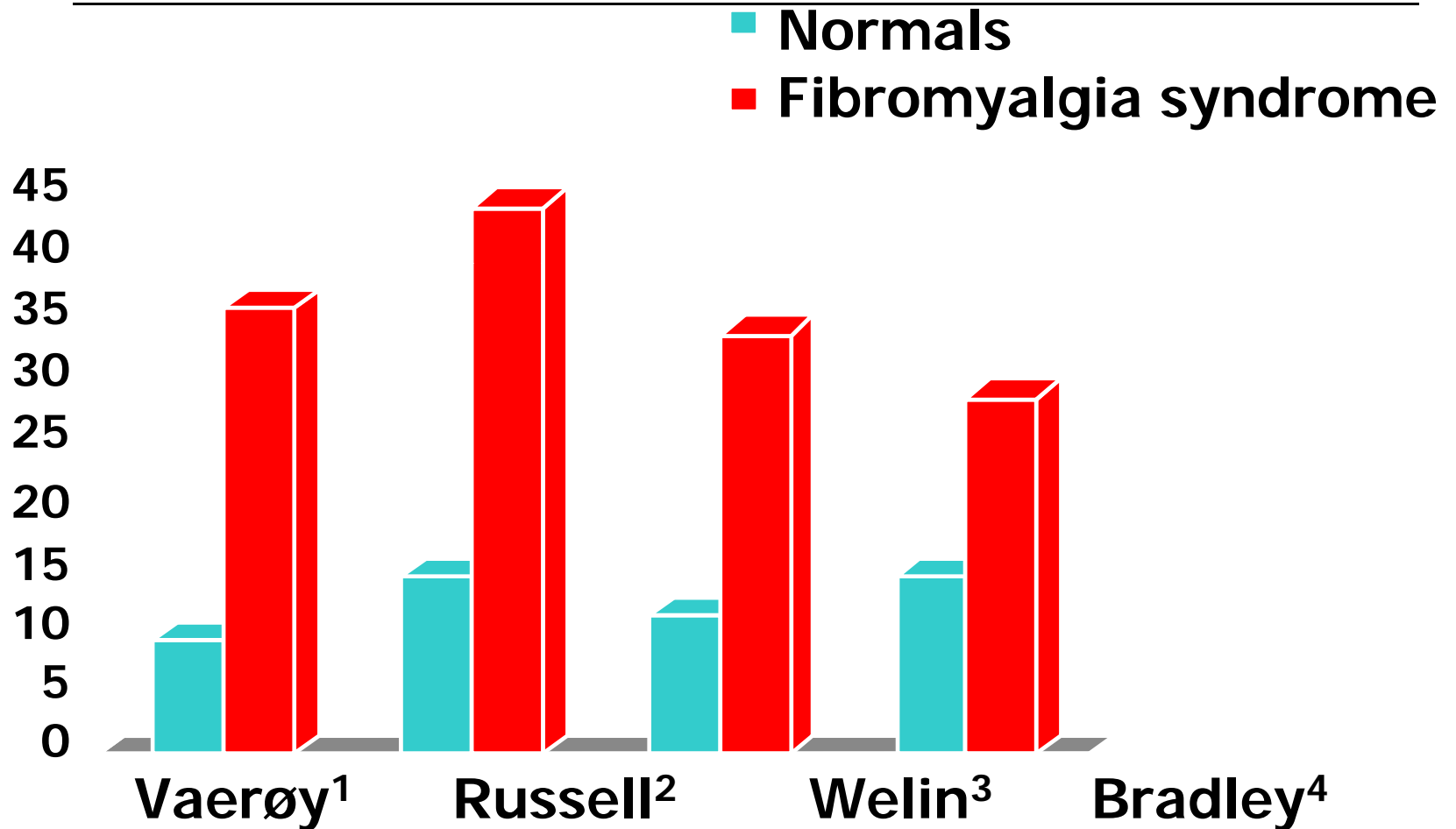
Déroulement de l'étude

- Questionnaires psychologiques
- Données électrophysiologiques de base
- Test de réflexe nociceptif ou sommation temporelle

Placebo, 0,5mg ou 1mg

- Données électrophysiologiques de base
- Test de réflexe nociceptif ou sommation temporelle

Fibromyalgia Cerebrospinal Fluid Substance P



1. Vaeroy H, et al. *Pain*. 1998;32:21-26. 2. Russell IJ, et al. *Arthritis Rheum*. 1994;37:1593-1601. 3. Liu Z, et al. *Peptides*. 2000;21:853-860. 4. Bradley LA, et al. *Arthritis Rheum*. 1999;42:2731-2732.