

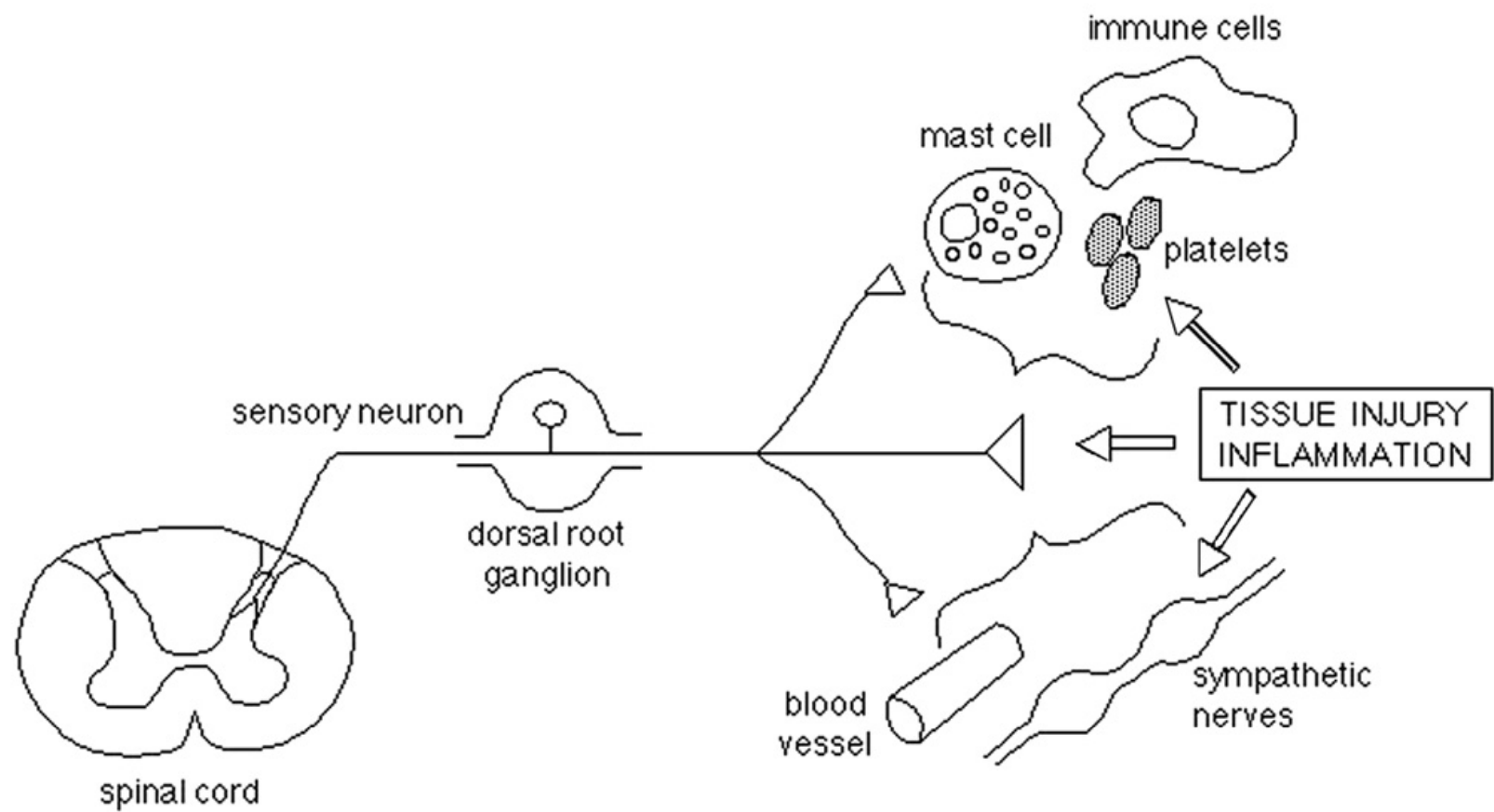
Novel Topical and Locally Acting Analgesic and Anti-inflammatory Agents

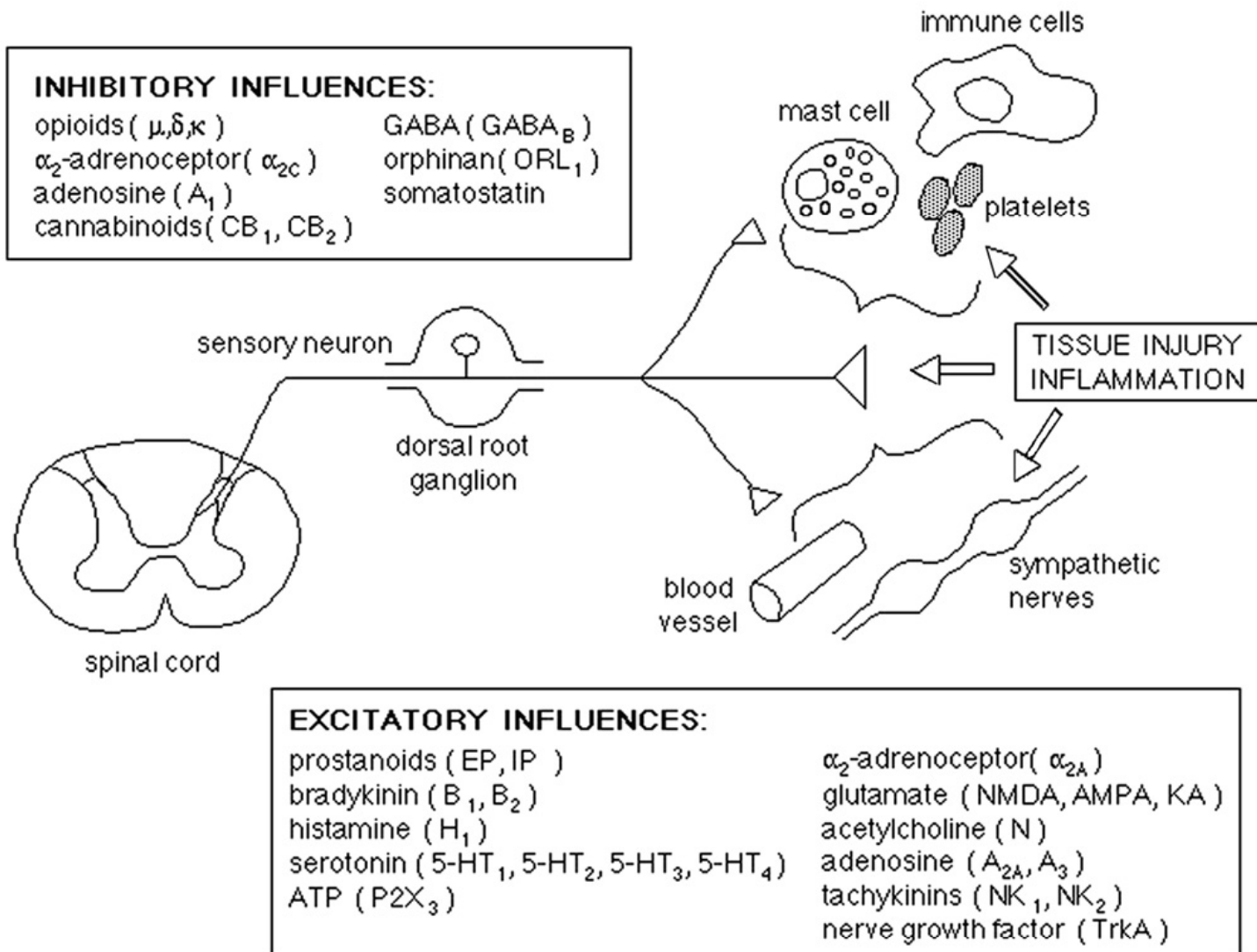
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PERIPHERAL DRUG DELIVERY

- **cream/gel/lotion OR patch**
for local peripheral topical application to somatic sites and/or joints
(drug properties, formulations matter)
- **injection OR infusion** for intra-articular applications *(perisurgical delivery)*
- low systemic drug levels; minimizes adverse effects and drug interactions
- localized toxicity reactions can occur

Topical Agents in the Treatment of Rheumatic Pain

Moore, Derry, McQuay (2008)
Rheum Dis Clin N Am 34: 415-432

RHEUMATIC
DISEASE CLINICS
OF NORTH AMERICA

-
1. **Topical NSAIDs** should be a core treatment for knee and hand osteoarthritis (NNT 4.5; cf. 3.8 musculoskeletal pain)
 2. **Topical capsaicin** should be adjunct therapy (NNT 8.1)
 3. **Rubifacients** (“counterirritants”) not recommended

*cf. EULAR guidelines for hand and osteoarthritis,
and OARSI guidelines for hip and knee osteoarthritis*

Novel targets for inflammatory pain

- **Ion channel antagonists/modulators** on sensory nerves
- **GPCR receptor agonists**, sensory nerves
- **Agonists/antagonists/modulators** on adjacent structures
- **Alter availability of endogenous mediators** (e.g. enzyme or transport inhibitors)

Novel targets for inflammatory pain

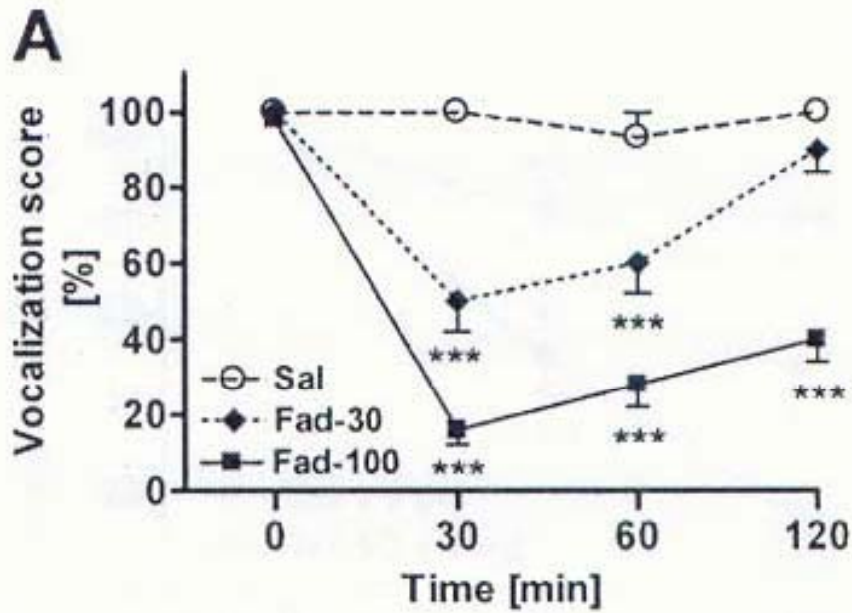
- α_2 -AR agonists
- 5HT antagonists
- antidepressants
- drug combinations

Fadolmidine (MPV-2426)

(α_2 -adrenoceptor agonist)

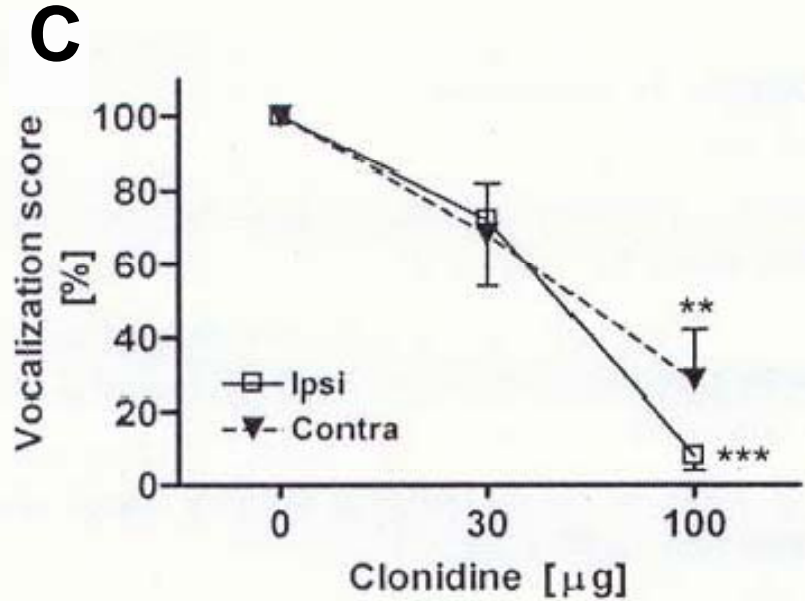
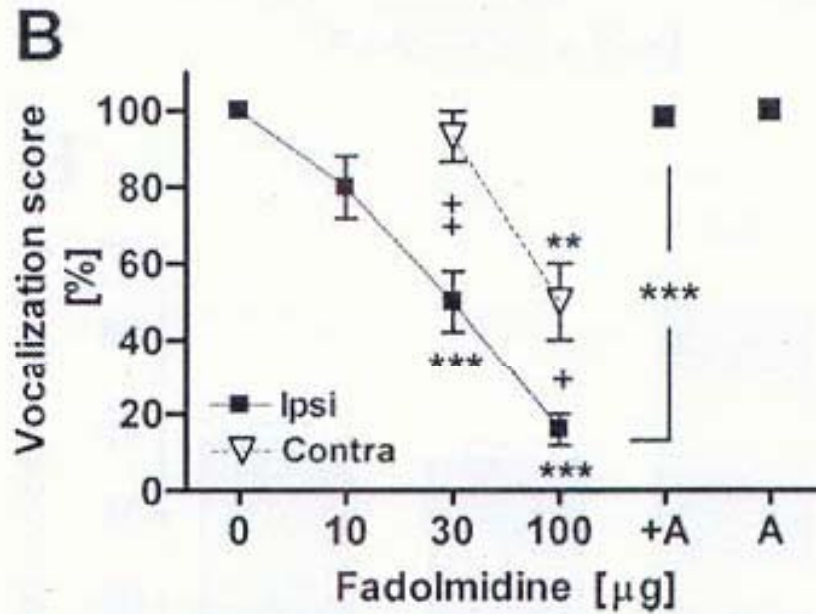
Ansah, Pertovaara (2007) Anesth Analg 105: 245-250

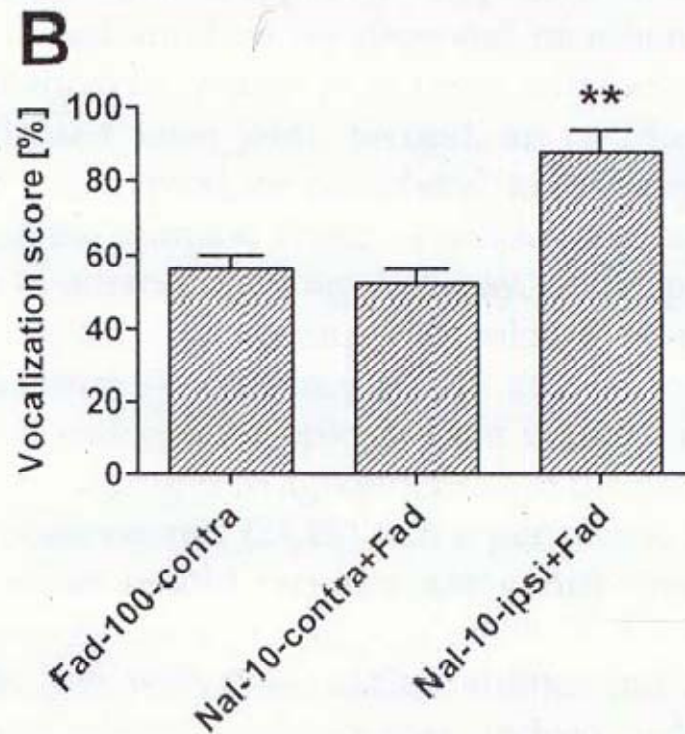
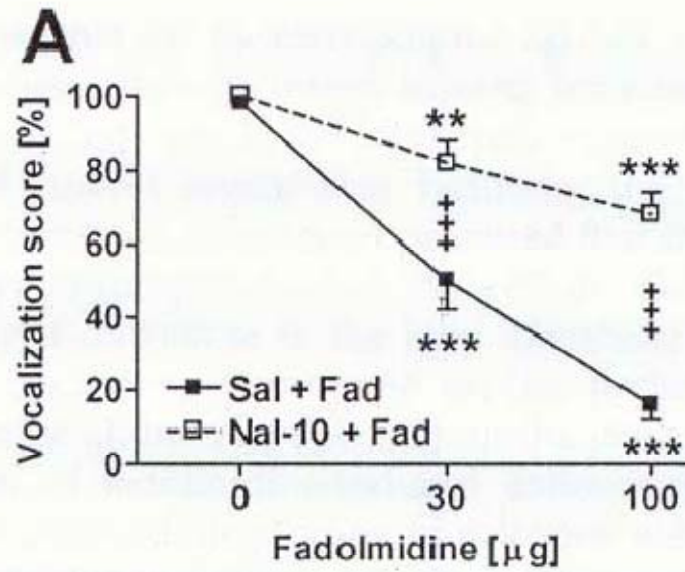
- **Clonidine** (1996-2001) and **apraclonidine** (2004) reduce arthroscopy-induced pain
- **fadolmidine** is selective and potent α_2 -AR agonist with poor penetration of blood brain barrier
- monoarthritis model (intraarticular kaolin and carrageenan) - vocalizations after flexion/extension
- fadolmidine given **intraarticularly**



Ansah, Pertovaara (2007)
Anesth Analg 105: 245-250

A= atipamazole (s.c.)





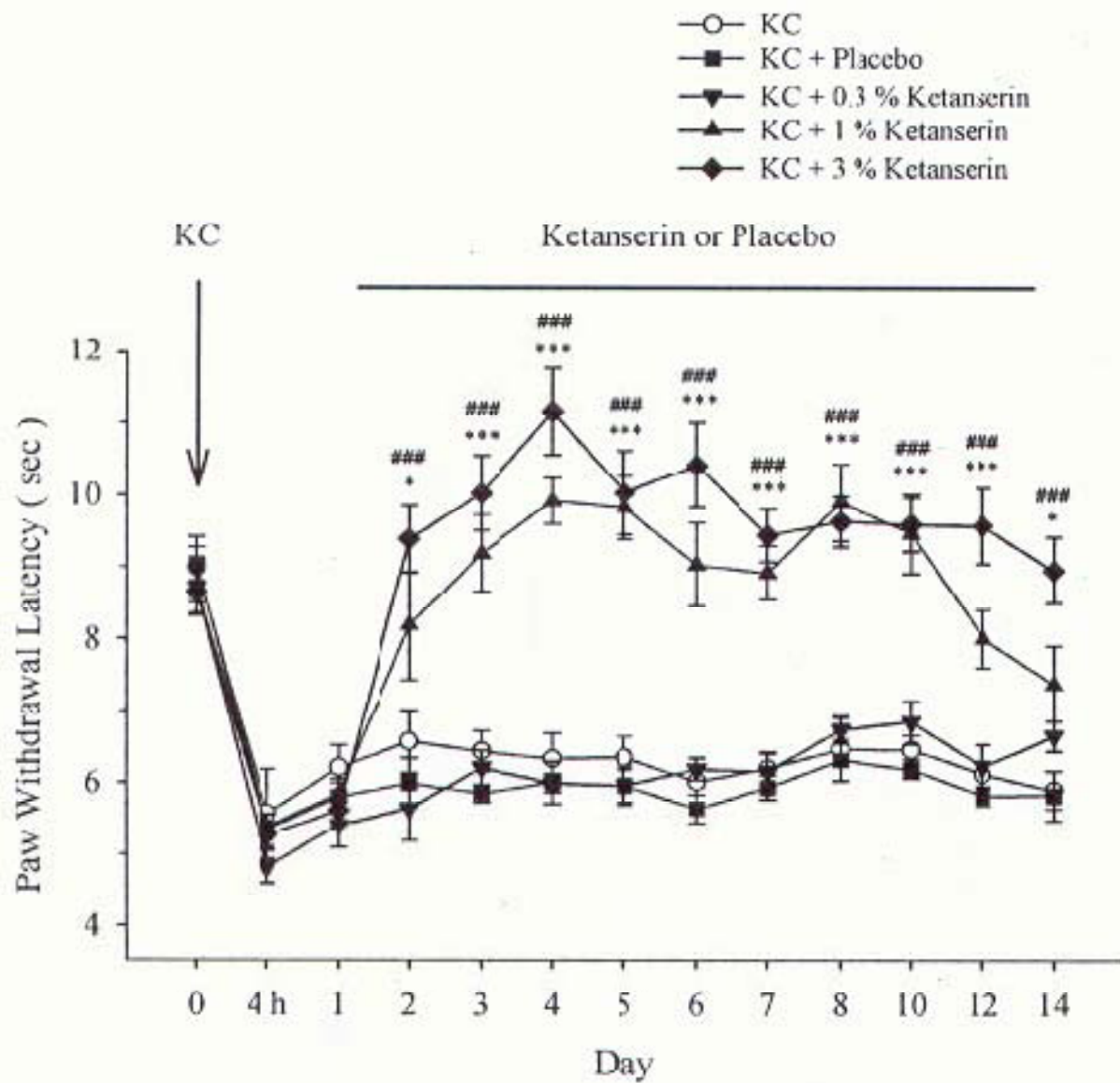
Ansah, Pertovaara (2007)
Anesth Analg 105: 245-250

Ketanserin

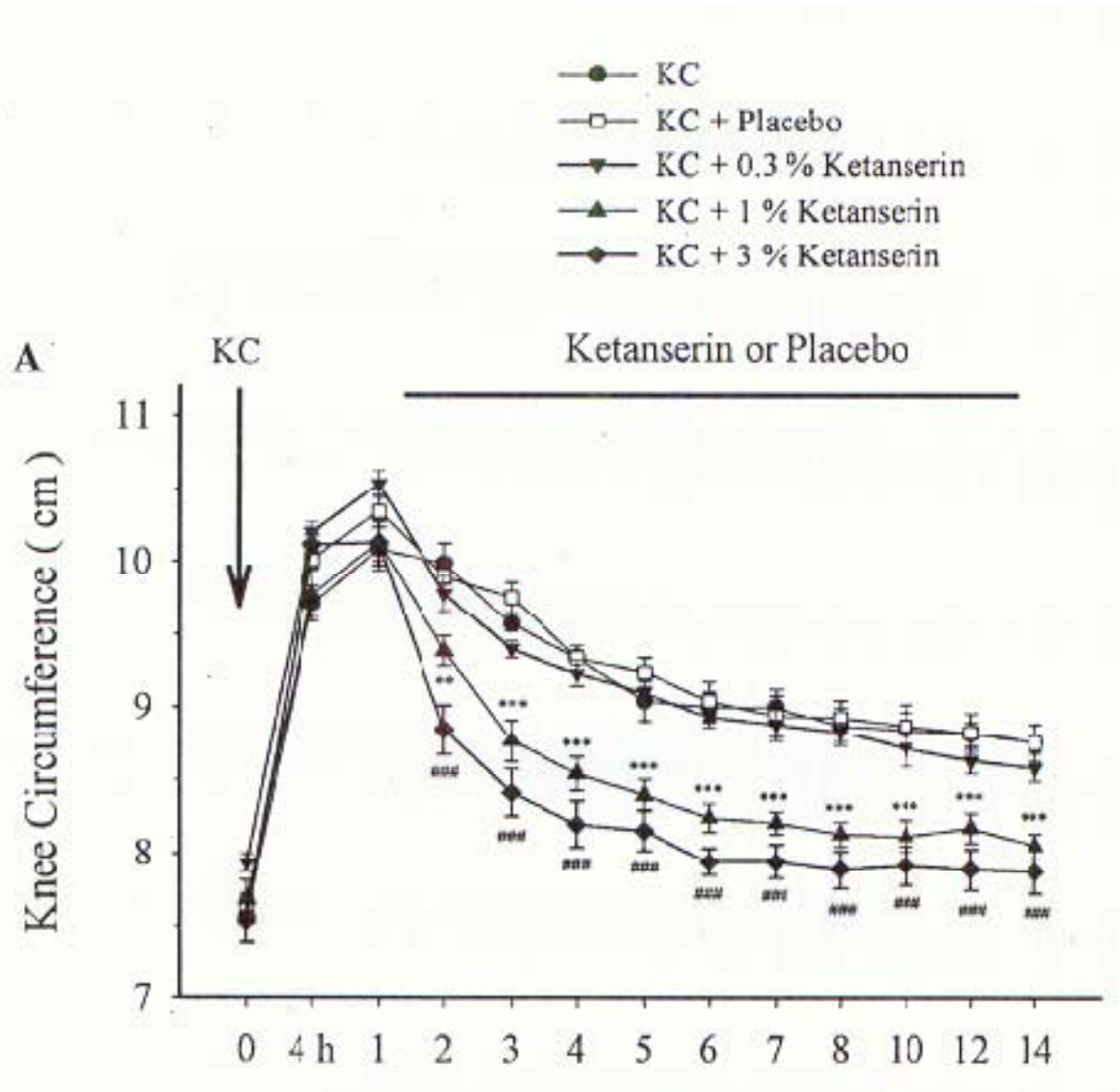
(5HT_{2A} receptor antagonist)

Hong Y, Ji H, Wei H (2006) Pain 124: 27-33

- 5HT mediator of pain and inflammation in arthritis; synovial 5HT levels increased in arthritis
- monoarthritis model (intraarticular kaolin and carrageenan) - paw withdrawal latency, joint size
- ketanserin given **topically** (drug 0.3-3% added to backing film, covered with liner, covers knee joint)



Hong et al (2006) Pain 124: 27-33

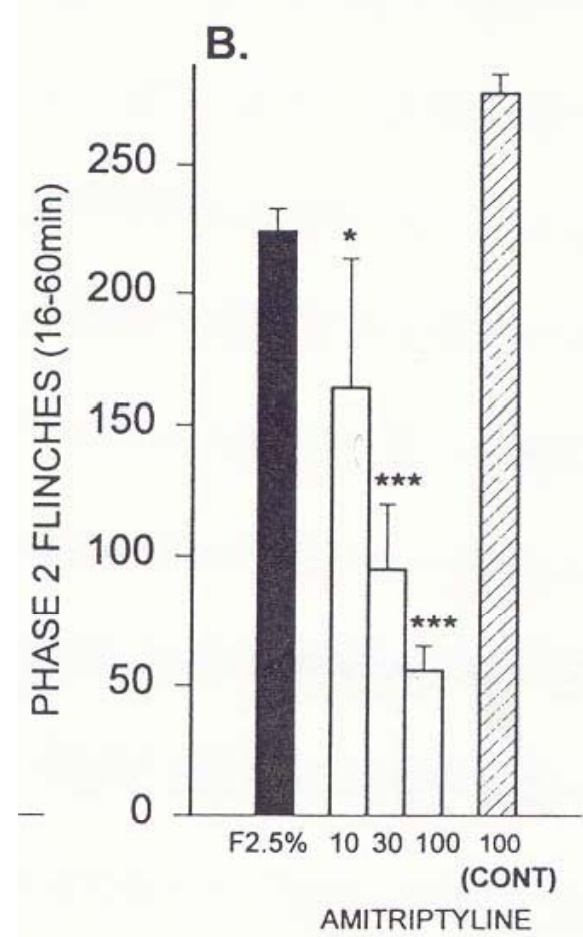
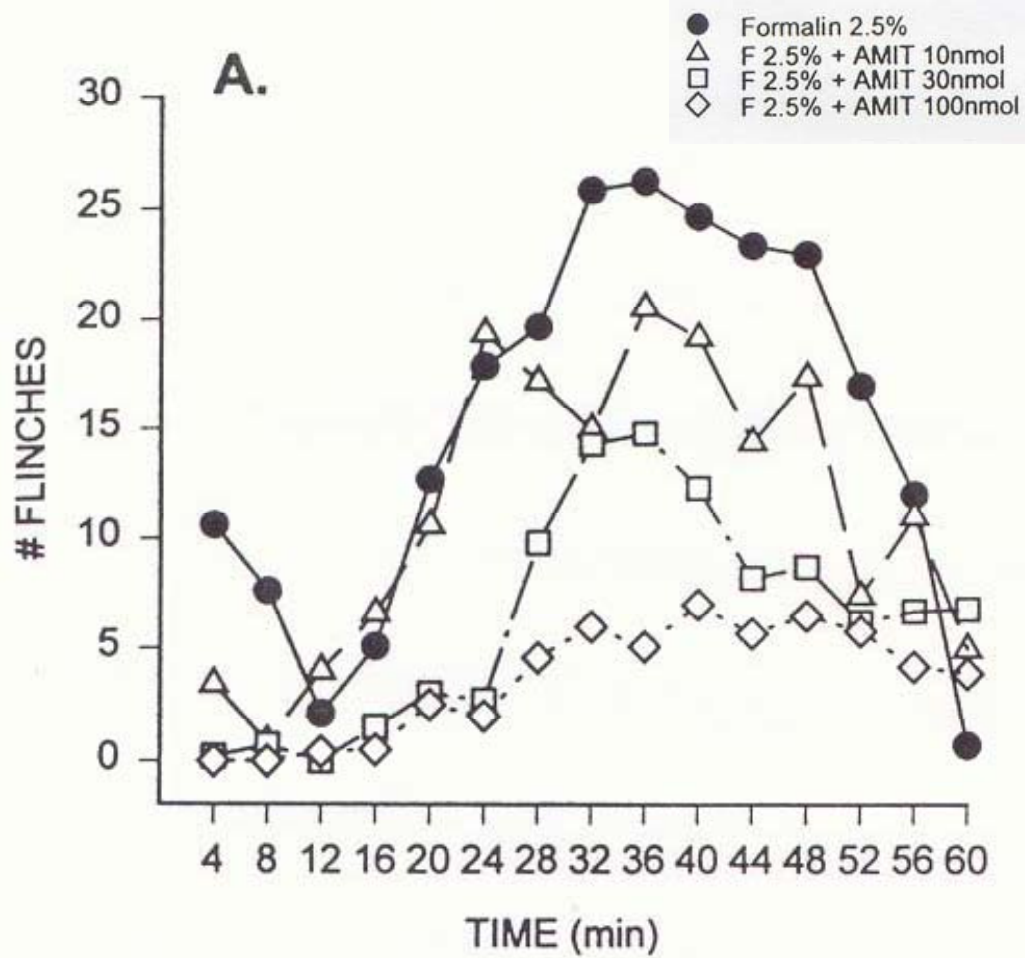


Amitriptyline

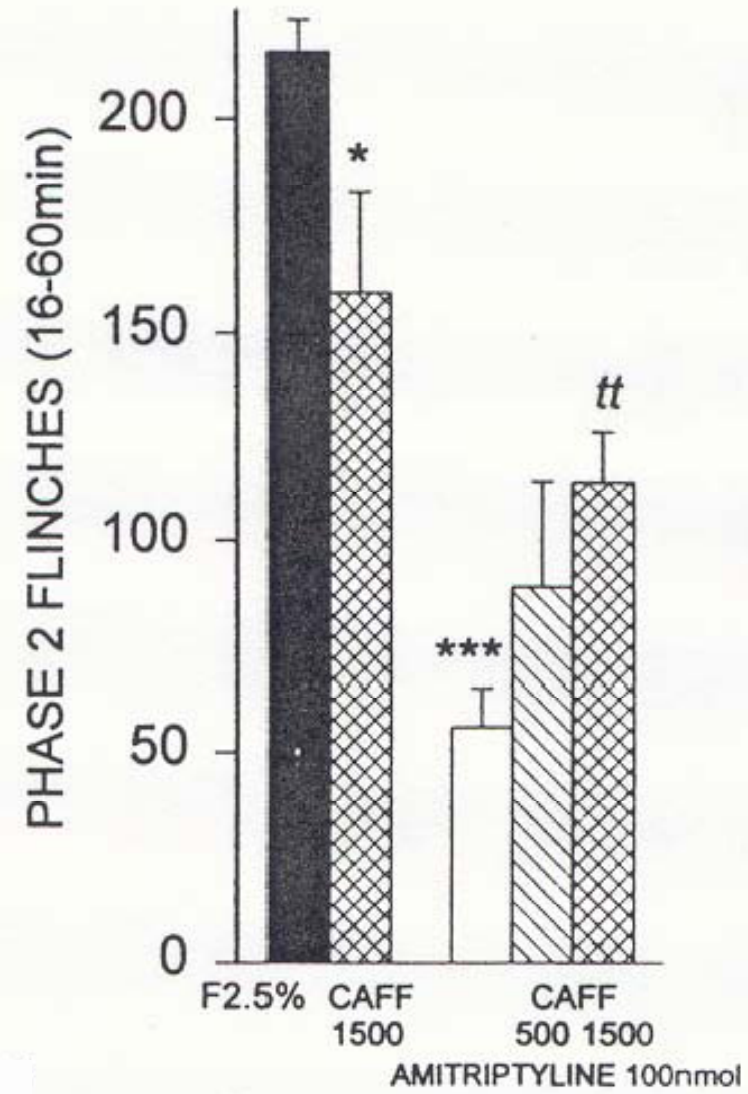
(NA/5HT transport inhibitor, also adenosine; inhibits Mus, α_2 AR, 5HT, H1 receptors; Na⁺ channel blocker)

Sawynok, Reid, Esser (1999) Pain 80: 45-55

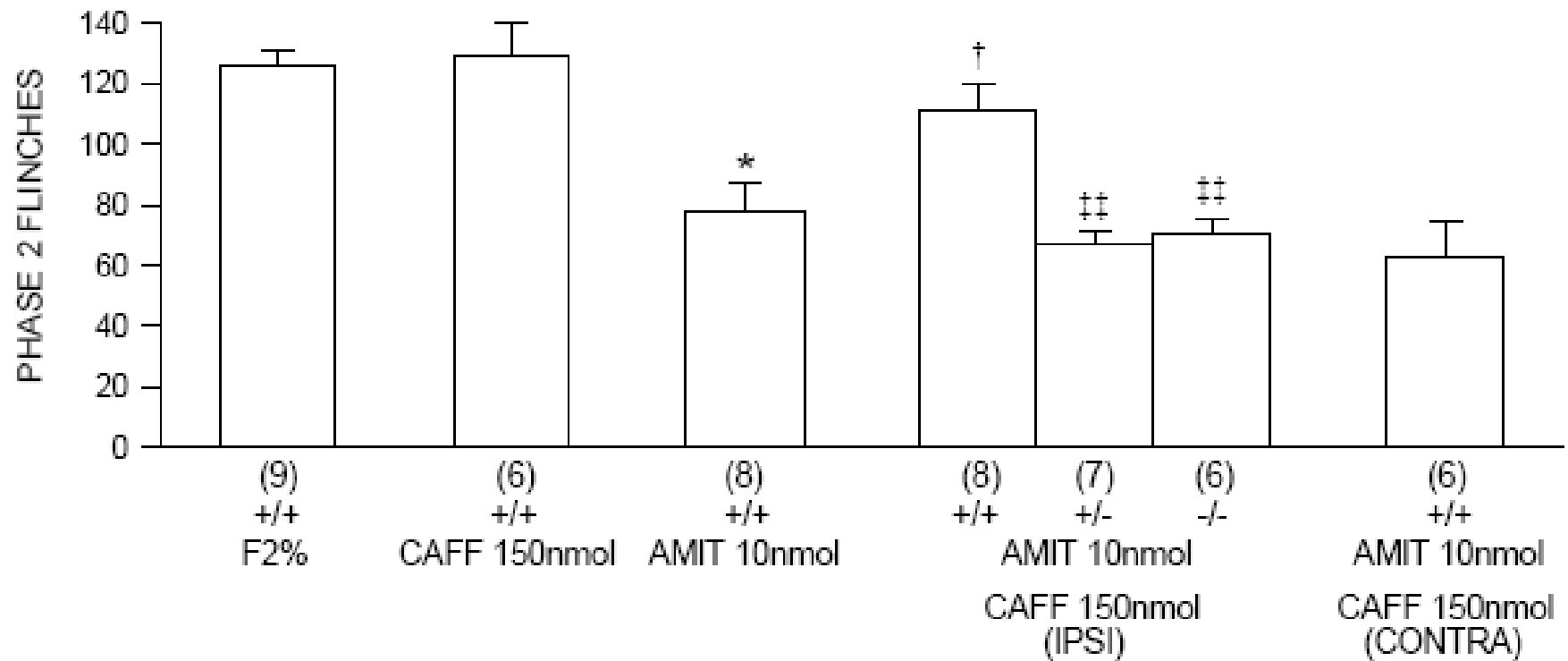
- 2.5% formalin model; model of ongoing/tonic pain; involves inflammation and central sensitization
- drugs co-injected s.c. with formalin (plantar side)
- pain behaviors for 60 min (flinching, biting/licking)



Sawynok et al. (1999) Pain 80: 45-55



Sawynok et al. (1999) Pain 80: 45-55



Sawynok, Reid, Fredholm (2008) Neurosci Lett 440: 181-184

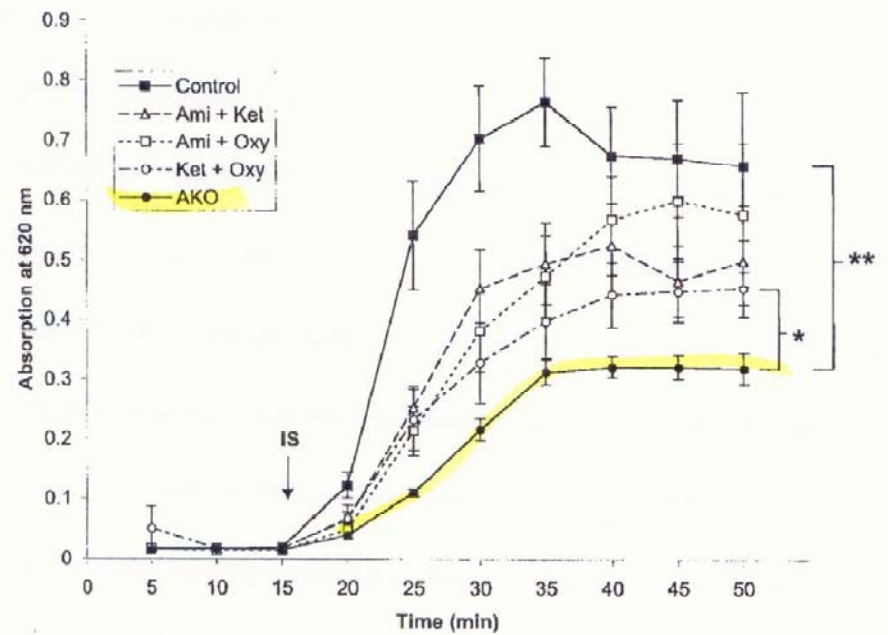
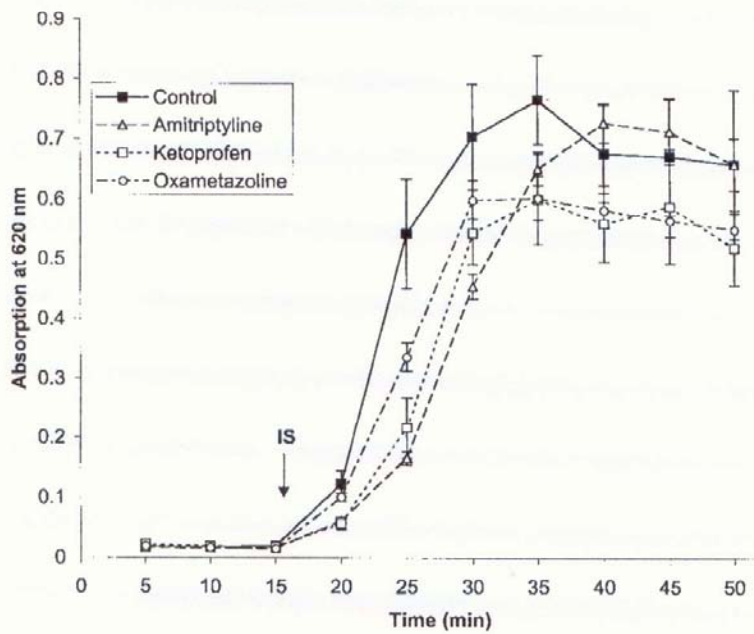
Drug combinations

ketoprofen, amitriptyline, oxymetazoline

(COX1/COX2 inhibitor; 5HT/H1 ant; α 2-AR/5HT_{1B/1D} ag)

Grond et al (2001) Anesth Analg 92: 1301-1306

- intraarticular perfusion of knee joint with bradykinin, 5HT, mustard oil
- measure absorbance, i.v. Evans blue dye (i.e. extravasation)



Grond et al (2001) Anesth Analg 92: 1301-1306

Combinations: Clinical Studies

ketoprofen, amitriptyline, oxymetazoline

Fanton et al (2008) Arthroscopy 24: 625-636

- ACL reconstruction surgery
(16 vehicle, 14 drug combination)
- significant effects on:
 - pain management
 - days to maximum flexion (6 vs 12d)
 - quadriceps strength testing d30
 - hamstring strength testing d30
 - return to work by day 7, 30

Combinations continued...

tramadol, ropivacaine, ketamine

*Ayoglu et al (2008) Arch Orthop Trauma Surg
(epub ahead of print)*

- arthroscopic meniscectomy (n=80)
- intraarticular tramadol (T), tramadol and ketamine (TK), ropivacaine (R), ropivacaine and ketamine (RK)
- TK group most effective in decreasing post-op opioid consumption

Combinations continued...

ketolorac, morphine, ropivacaine

Axelsson et al (2008) Anesth Analg 106: 328-333

- shoulder surgery (n=51)
- group 1: intraarticular K + M + R
group 2: intraarticular saline, i.v. K
group 3: intraarticular saline
- group 1 has:
 - lower post-op pain at rest and with movement
 - larger time to post-op analgesia
 - greater patient satisfaction

Conclusions

- (1) Topical (cream or patch/bandage) and intraarticular drug applications have potential as analgesics in inflammatory pain
- (2) Compartmental drug delivery systems; low systemic levels and minimal adverse effects
- (3) Peripheral complexity of signaling provides several potential novel drug targets; combinations represent further strategy

Disclosures / Acknowledgements

- Speaker holds IP for antidepressants as topical analgesics
- Speaker has conducted research funded by Gensia, Proctor & Gamble, Abbott, Epicept
- Research cited in presentation (JS) supported by Canadian Institutes of Health Research