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Evaluating Pain Mechanisms and Targets with Human Experimental Models

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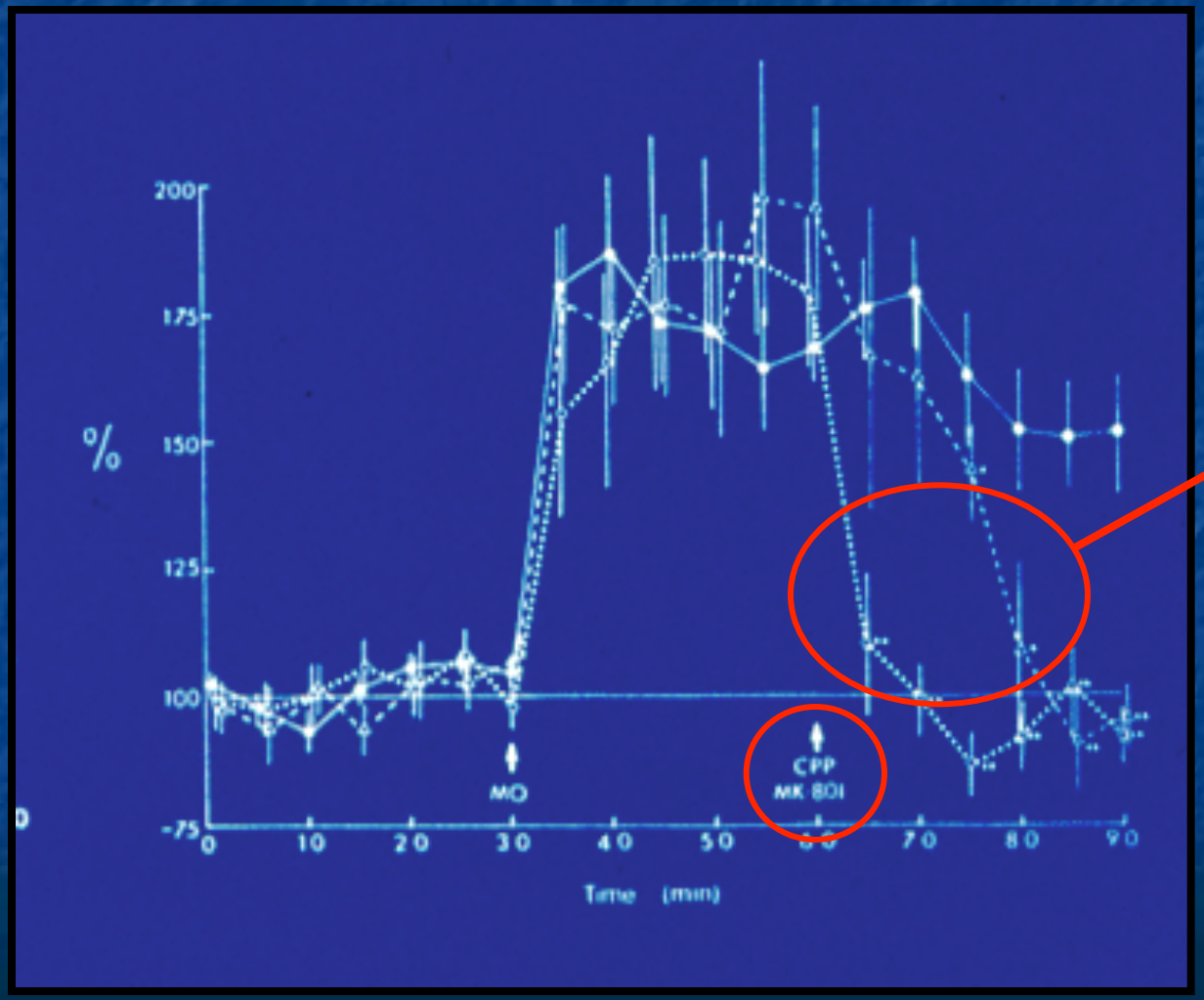
Evaluating Pain Mechanisms with Human Experimental Models

This is basic research – obviously a great idea. We need more of it, especially in pain patients.

For example…….

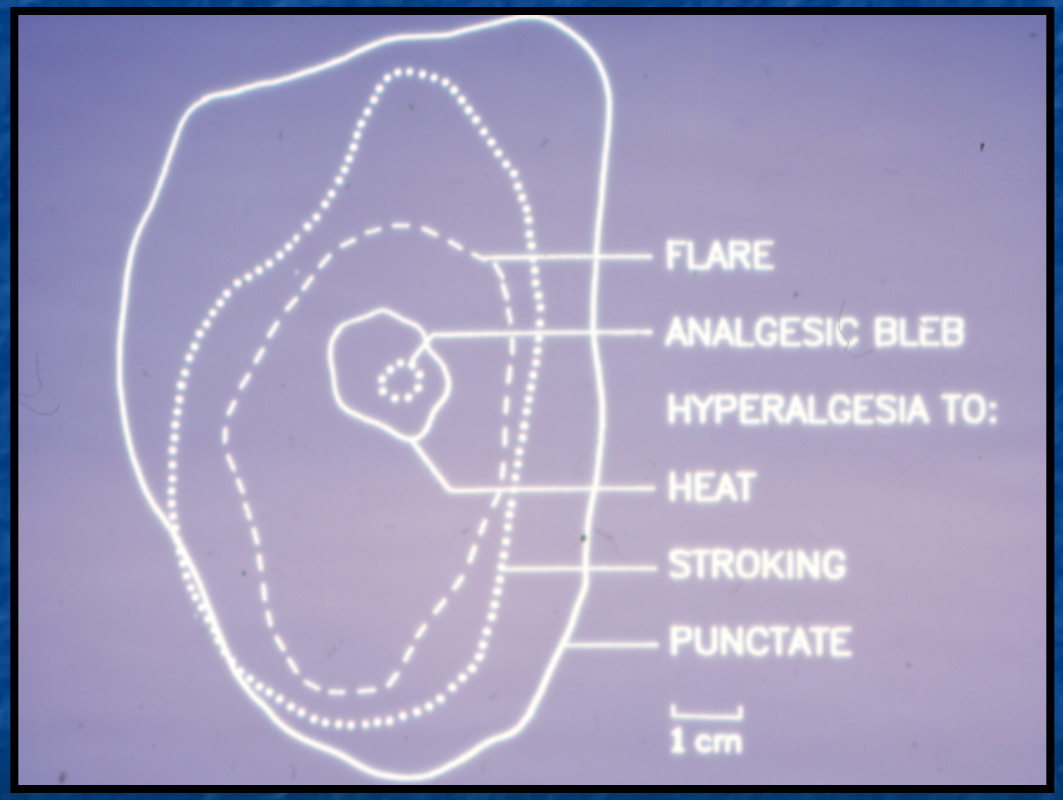
Central sensitization evoked by C-nociceptor input in rat



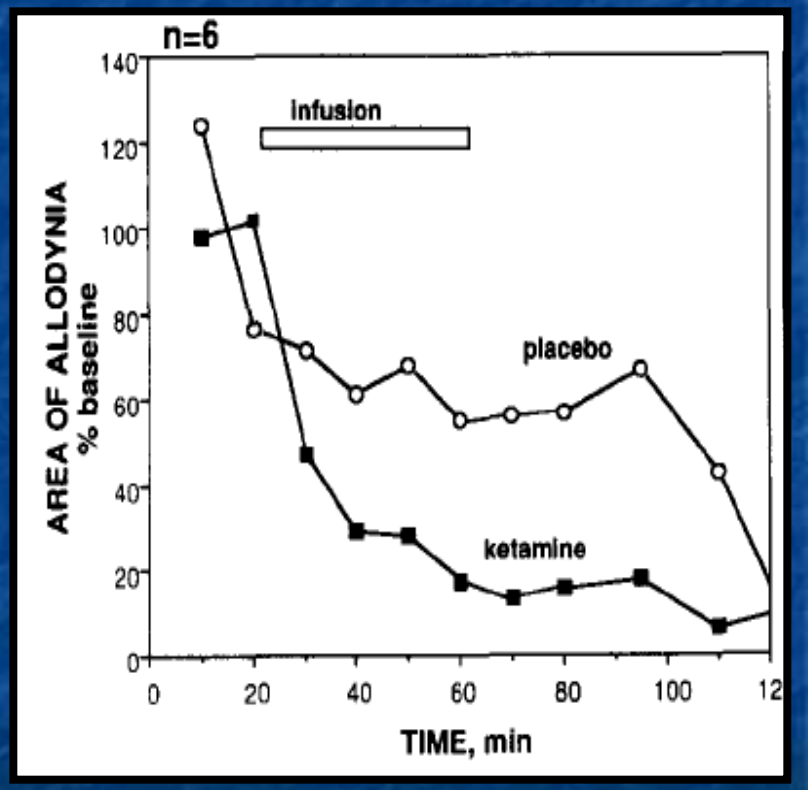
NMDAR block

Woolf & Thompson, 1991

Central sensitization evoked by C-nociceptor input in man



LaMotte et al., 1991



Park et al., 1995

Evaluating Pain Targets with Human Experimental Models

This is usually not basic research, but rather a part of an attempt to improve drug development.

The idea is that a relevant pathological mechanism can be produced (temporarily!) in a normal human subject.

Can we do this? Yes, but to a very limited extent.

Evaluating Pain Targets with Human Experimental Models

Primary afferent sensitization

This can be easily studied in normal human subjects – capsaicin, sunburn, etc.

OK for inflammatory pain conditions, but is there any evidence for primary afferent sensitization in neuropathic pain conditions?

Evidence for primary afferent sensitization (PAS) in neuropathic pain conditions:

1. *Allodynia & hyperalgesia – Yes, but these could be CNS effects.*
2. *Early stage CRPS-I looks like PAS, but DPN and PHN do not. Note relative rarity of heat-hyperalgesia.*
3. *In man, microneurography has shown spontaneous discharge in sleeping C-nociceptors, but no evidence of change in thresholds or SR functions in any nociceptor.*
4. *In rat, evidence for up-regulation of transducers (e.g., TRPV-1) but no single-fiber recording evidence for PAS.*

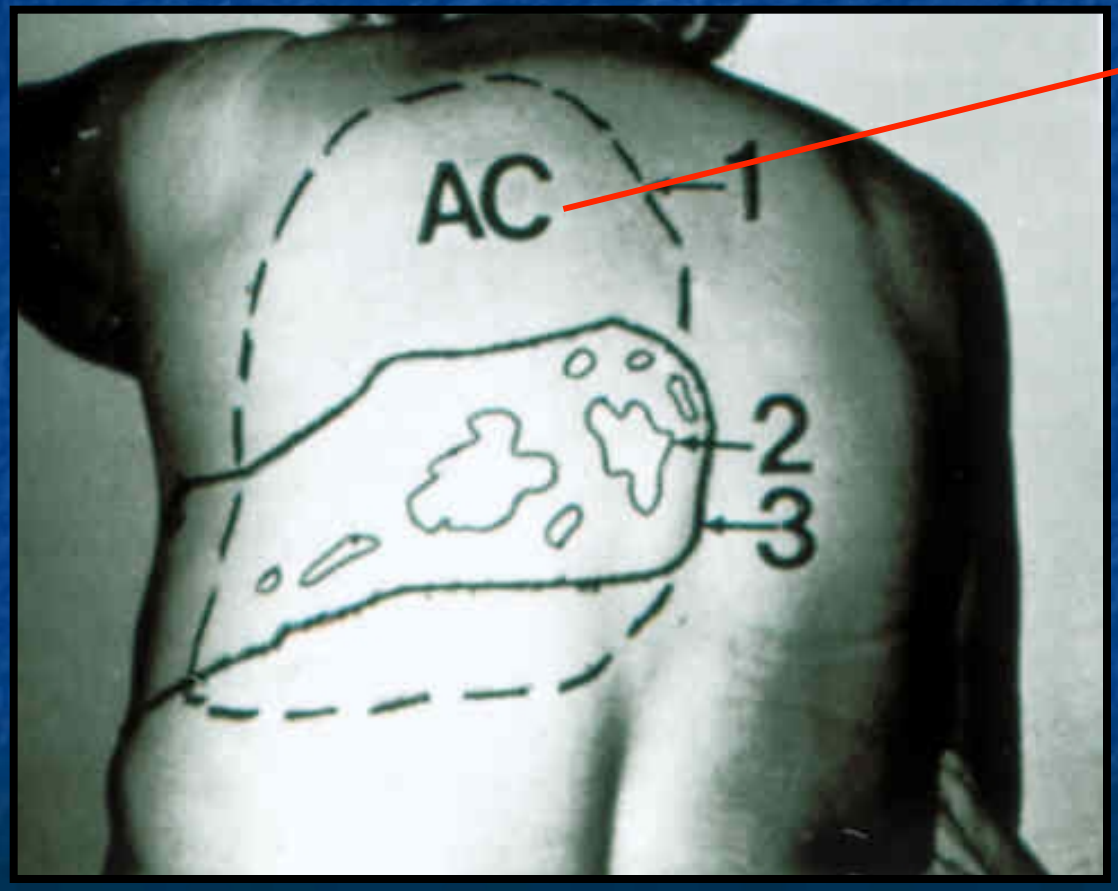
Evaluating Pain Targets with Human Experimental Models

C-nociceptor input-evoked central sensitization

We can study this too (e.g., the capsaicin model).

BUT only limited evidence that central sensitization is a contributory factor in some neuropathic pain conditions.

Evidence that central sensitization is at least a contributory factor in some neuropathic pain conditions



Watson et al., 2001

PHN: Dynamically modulated zone of allodynia surrounding infected dermatome.

Similar in CRPS I-II.

Nothing like this in DPN or CIPN distal symmetrical polyneuropathy.

If it is not primary afferent sensitization or central sensitization, then what causes the pain?

I don't know and neither does anyone else.

You can make experimental models of a disease, but if you do not know what the mechanism is, then you can not model the mechanism without the disease.

For drug discovery, why even bother with experimental models in normal subjects?

- You can't trust mice and rats. There may be pathological pain mechanisms unique to man.
  Possible, but I do not know of any evidence that this is true.

- But it has worked before.
  Has it?

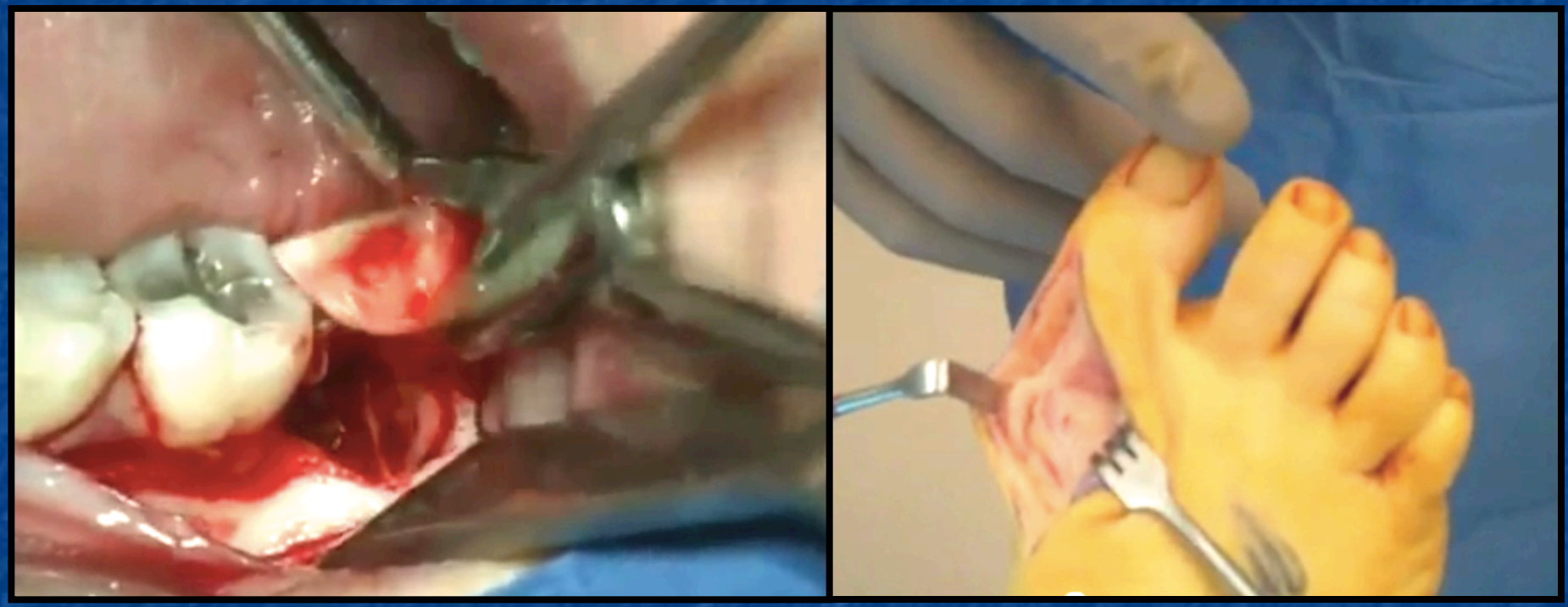
It has worked before….

Third molar extraction model.

Bunionectomy model.

Very successful in the development of NSAIDs and their combination with opioids

Are these "models" of post-surgical pain and inflammation?



No– they <u>are</u> post-surgical pain and inflammation!

It has worked before…

No, it has not worked before.

No analgesic has ever had a development program that involved tests of efficacy in normal human subjects (closest-Qutenza®)

Has the development program for a drug for any disease ever had an important efficacy trial in normal human subjects?

Evaluating Pain Targets with Human Experimental Models

Experimental pain models in normal human subjects will make drug development faster and cheaper.

Nonsense. It will just add another inherently indecisive step before the test in patients.

Forget about human experimental models (at least for now). Go straight to the patients!

It is no more than a convenient fiction that we know a drug's mechanism of action and that we know that mechanism is relevant for any particular pain condition.

Go to the patients!
Let yourself be lucky!

If mechanisms are unknown, how does one proceed?

Do Phase Ib pilot studies in small groups (ca. n=20) of Pts with various conditions:

DPN, PHN, CRPS, CIPN, VVS, idiopathic small fiber neuropathy, MS;

AND assess Sx individually: touch-allodynia, cold-allodynia, etc.