# Filmpje: Pijnprikkel



### Development of pain system









## Neuro-anatomy



### Neurotrophins and nociceptor development



Marie Fitzgerald et al. Nature 2005;6:507-520

Schematic diagram of the synaptic changes that take place in the superficial laminae of the dorsal horn over the first 2 – 3 postnatal weeks



Marie Fitzgerald et al. Nature 2005;6:507-520



Fitzgerald et al. 2005

# Activity-dependent development in spinal cord sensory connections



Marie Fitzgerald et al. Nature 2005;6:507-520

### Influencing factors in a clinical setting

### Environment?

Medication Opioids/sedatives?









# What outcome data should at least be assessed ?

- - Detection thresholds?
- - Pain thresholds?
- - Suprapain sensitivity?



#### **Neonatal period**

#### 8-9 years

#### Surgery group (n=57)

 $\leq$  3 months of age

Abdominal/ thoracic surgery

### Mechanical ventilation group (n=53)

Artificial ventilation >5 days

No morphine

#### ECMO group (n=60)

Meconium aspiration / sepsis Morphine >5 days

#### **Follow-up**

Guidelines Dutch Paediatric Association for follow up of critically ill newborns

#### **Prospective**

- Illness
- Development
- Hospital admissions
- Surgical procedures

#### **Outcome**

#### **Detection threshold**

#### Pain threshold

#### Suprapain threshold

Schouw et al. In preparation



### Assessment pain sensitivity: three different body locations

Postoperative

**ECMO** 





### **Respiratory insufficiency**



### Neonatal pain exposure: developmental window

#### Premature neonate

#### Term born neonate

2-3 months old







hypo sensitive thermal detection & hyper sensitive pain than term born counterparts

Hypo sensitive thermal detection &

Hyper sensitive pain than when operated upon at 2-3 months of age



#### 💮 FOCUS ON PAIN

### REVIEWS

THE DEVELOPMENT OF NOCICEPTIVE CIRCUITS

...."Tissue damage during a critical period of newborns can cause prolonged alterations in somatosensory function, which last into adult life"...

Department of Anatomy and Developmental Bology, Wellcome Pain Consorting, Outward Velocation, Outward Vector of Vector Weart and UCT canails mefitgerakiguel.ac.uk doi:01.03/arm1701

This review focuses on the underlying organization numon C- and B-expressing (TrkC' and TrkD\*) neu and strengthening of nociceptive circuitry in the dorsal ronsare born first, followed by small-diameter TrkA' horn during the first postnatal weeks and on recent neurons22. Recently, an even later wave of nock-splive data that show how that circulary might be altered by neutons has been shown to arise from boundary cap sensory inputs in early life. It begins with the specificells, which are neural crest derivatives that migrate cation of nociceptive neurons - recent studies have down the root from the dorsal root entry zone. All identified key molecular pathways that control the these neurons require neurogenin 1 or 2 (NGN1/2) genesis of spinal no ciceptive circuits. It then traces the - two neuronal determination genes that encode formation of functional synapses, neural circuits and basic helix-loop-helix (bHLE) transcription factors

NATUREREVIEWS NEUROSCIENCE

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 Conclusion: mainly based on studies in animals

 Pain studies in human infants: max. follow-up ≤ 3 years

Fitzgerald Nature Reviews 2005

# Descending pathways



# Gate Control Theory





# Are (pre)term born children capable of processing pain at a cortical level?



Slater et al. 2006

### **Pain Threshold and PCA**



Fitzgerald et al. Pain 1989; 39: 31-36

Fitzgerald et al. Pain 1989; 39: 31-36

### **Sensitisation versus Habituation**



### THE PROBLEM OF SENSITISATION AND SENSITIVITY

- Effects of previous potentially painful events on
  - pain threshold
  - distribution of opioid receptors
  - neurophysiological parameters
  - long-term behavioural problems
- Genetic heterogenecity
  - genetic defects  $\rightarrow$  transgenic mice
  - DNA fingerprints  $\rightarrow$  mutation analysis

### THE PROBLEM OF SENSITISATION

### **Experimental approach in newborn rats**

### Human experience in the newborn period





Ruda MA et al. Science 2000;289:628-630





### **TIMING MAKES A DIFFERENCE**



### Research needs (NIH\FDA conference april 2004)

- Empiric foundations for composite measures in the youngest neonates (22-26 weeks)
- Understanding autonomic responses and how they change in the youngest neonates
- Need for assessment scales for chronic\ongoing pain
- PK\PD data of all analgesics
- Incorparate models which show patterns of response

### Pediatric pain, the research agenda: <u>future (2005- ?)</u> Solutions are near and "far away"

**Profound cognitive impaired** 

- children

#### elderly people

