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**Chronic inflammation and pain:
Assessment of c-Fos and ATF-3 as markers of spinal
neuronal activity in a pain model of rheumatoid arthritis**

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Molecular Pain Group

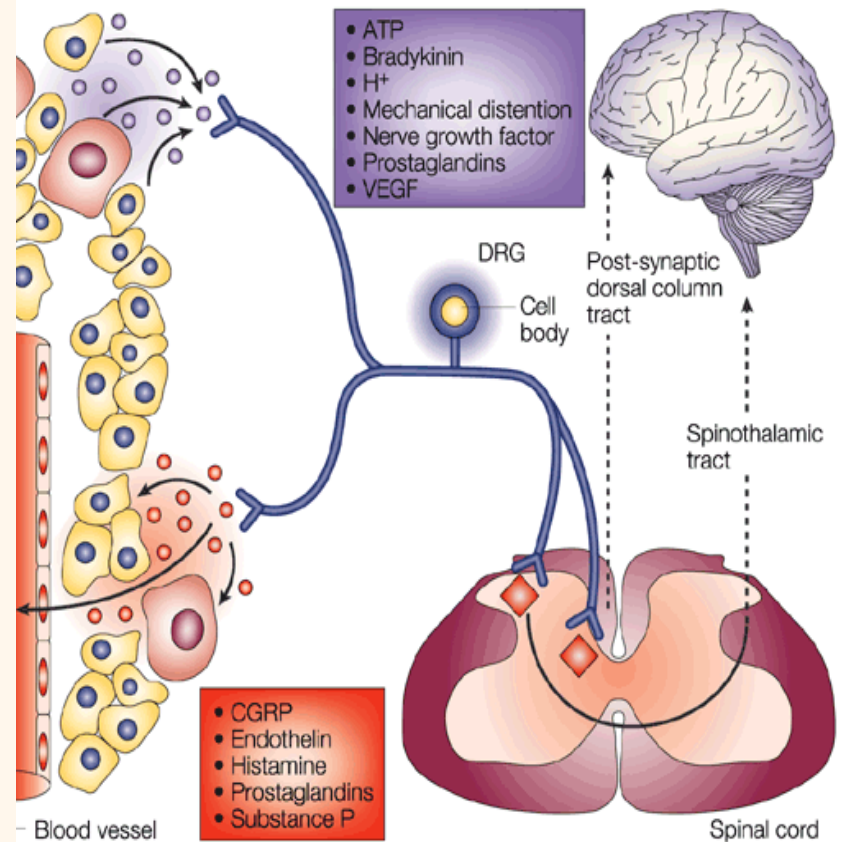
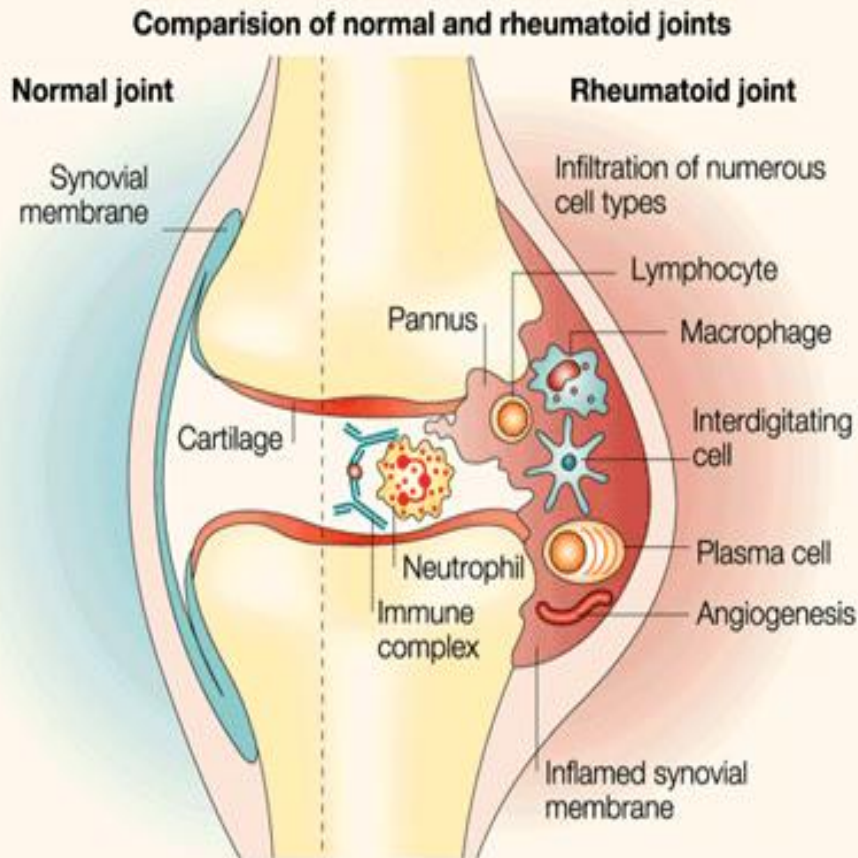
Department of Physiology and Pharmacology

Introduction

Pain in chronic inflammatory diseases, such as rheumatoid arthritis (RA), is a major clinical problem



Even after anti-inflammatory treatment **chronic pain still remains**

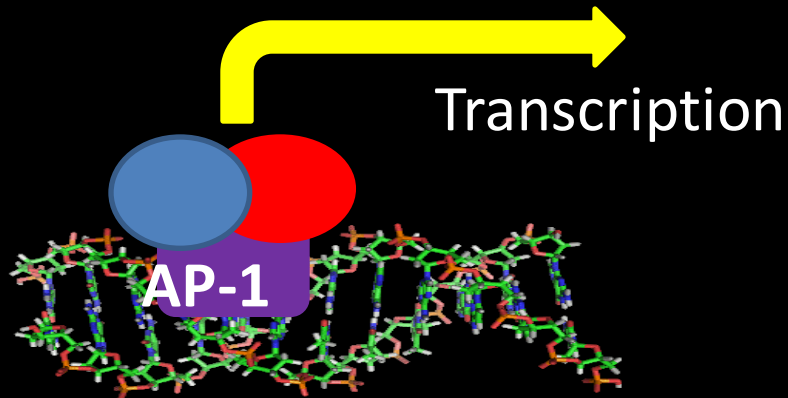
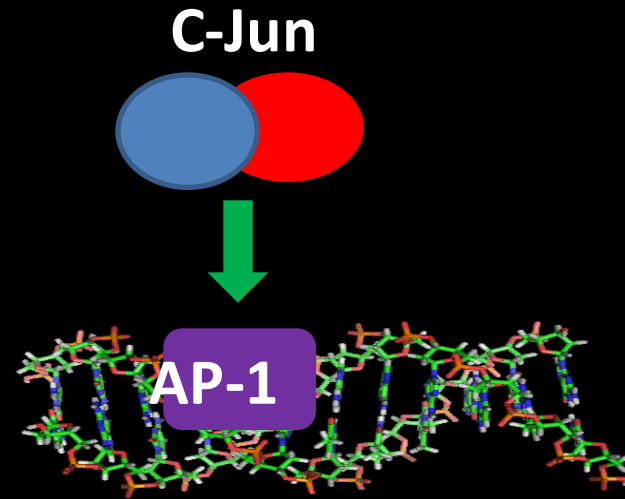
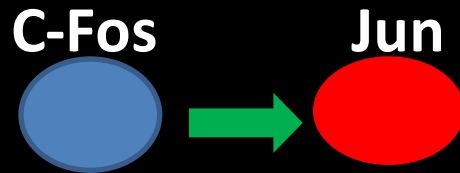


Feldmann, M. (2002). Development of anti-TNF therapy for rheumatoid arthritis. *Nature Reviews Immunology*. 2: 364-371

Mantyh, P. W., Clohisy, D. R., Koltzenburg, M., Hunt, S. P. (2002). Molecular mechanisms of cancer pain. *Nature Reviews Cancer*. 2: 201-209

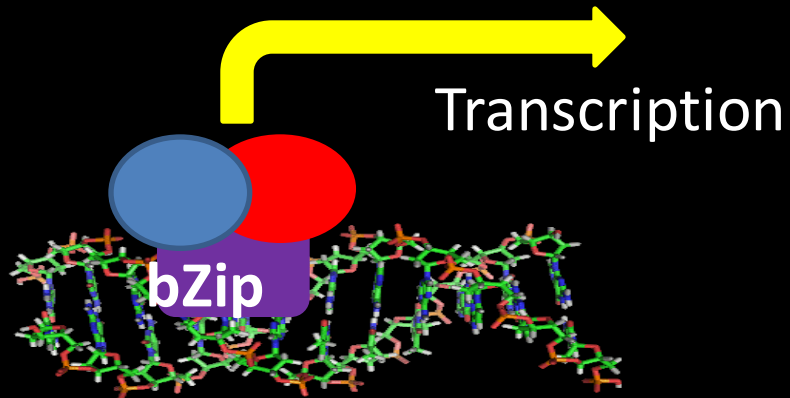
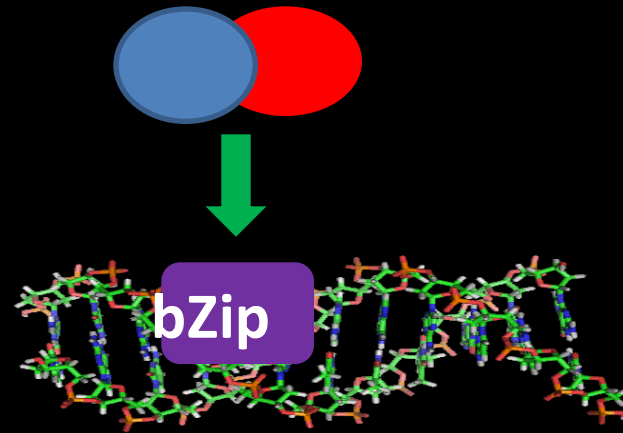
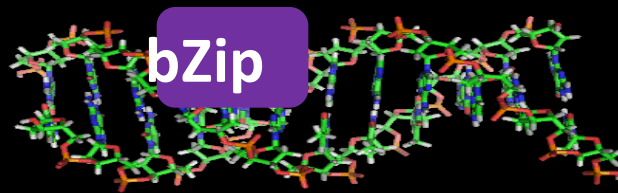
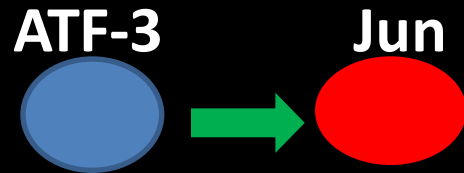
Chronic inflammation → neurons hypersensitive → chronic pain

C-Fos

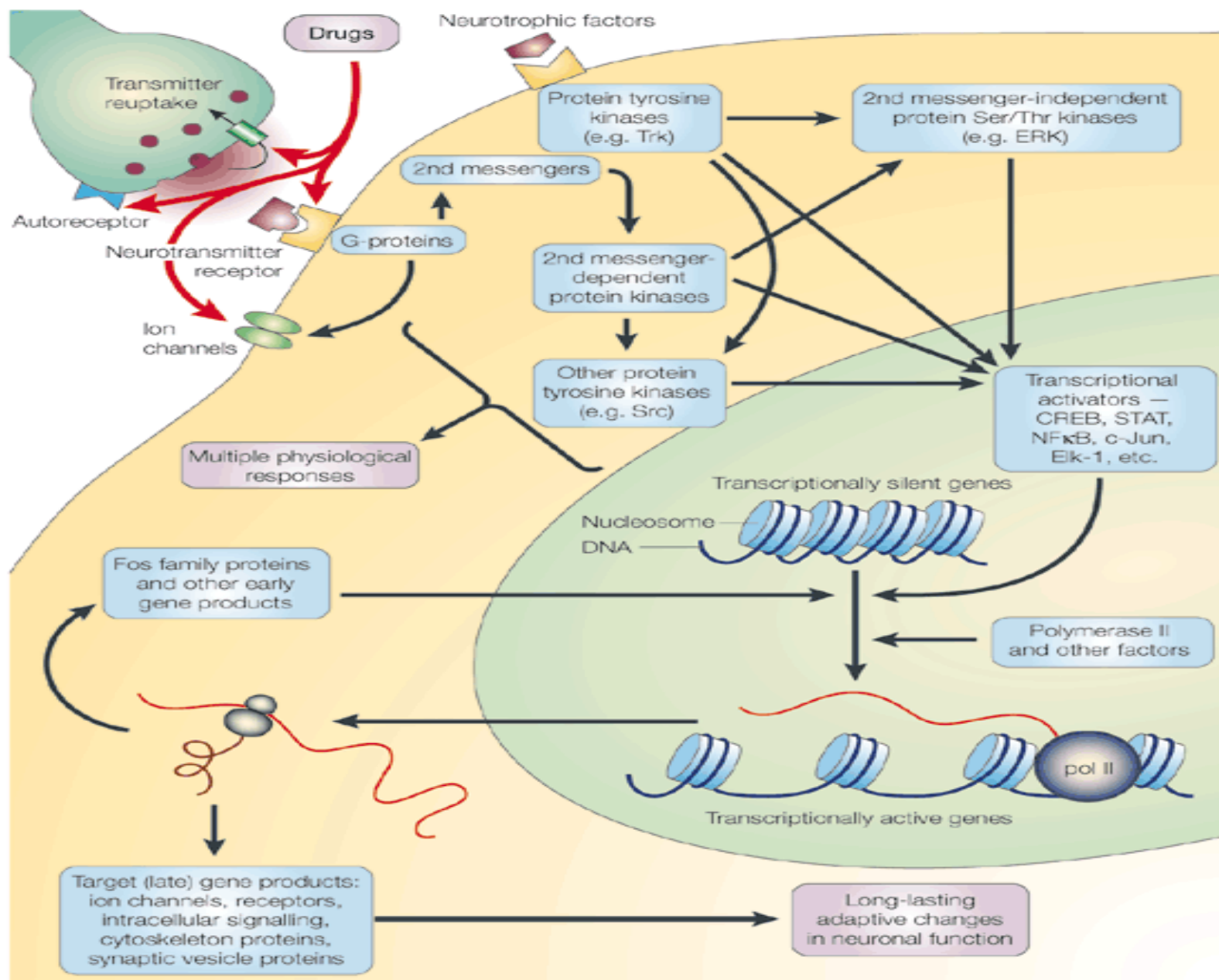


- Increased neuroexcitability
- Cellular adaption
- Proliferation
- Differentiation
- Defense against cell damage

ATF-3



- cyclic AMP-dependent transcription factor
- stress, injury



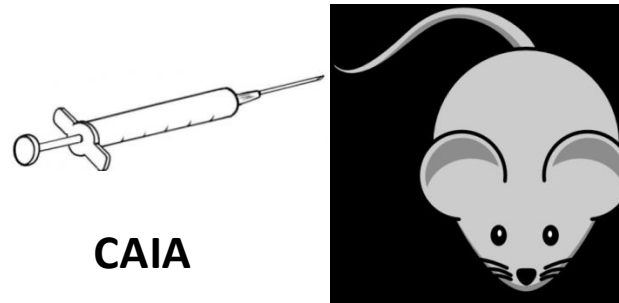
Aim

**Is there a change
in the number of c-Fos/ATF-3 positive
neurons in the dorsal horn of the spinal
cord during and after RA inflammation?**

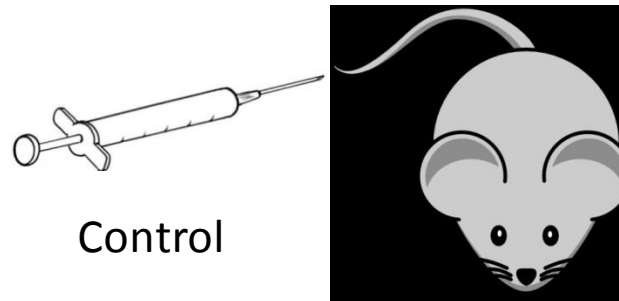
Method

Mouse model:

Collagen II
Antibody
Induced
Arthritis



CAIA



Control

mAbs



Collagen II



Macrophages/
Neutrophils



Cytokines

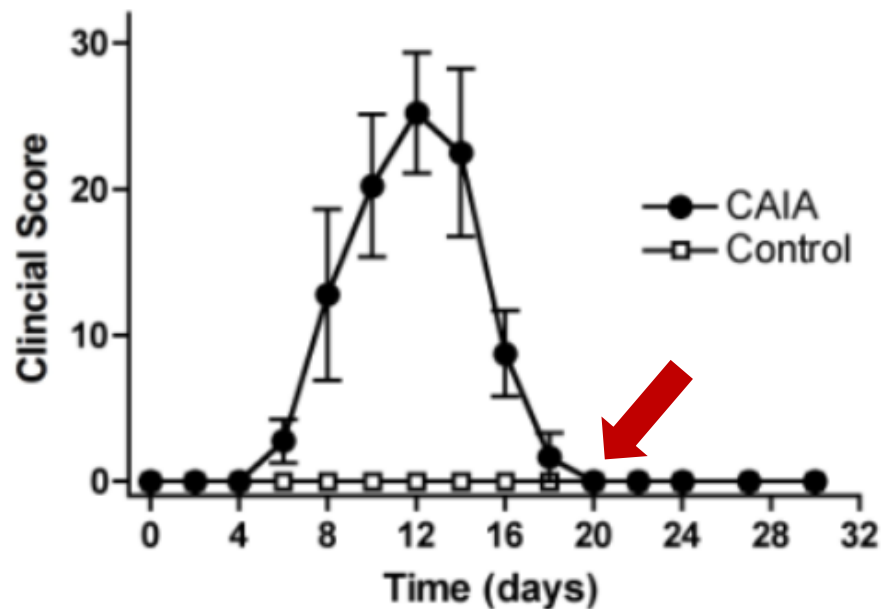


RA

Results

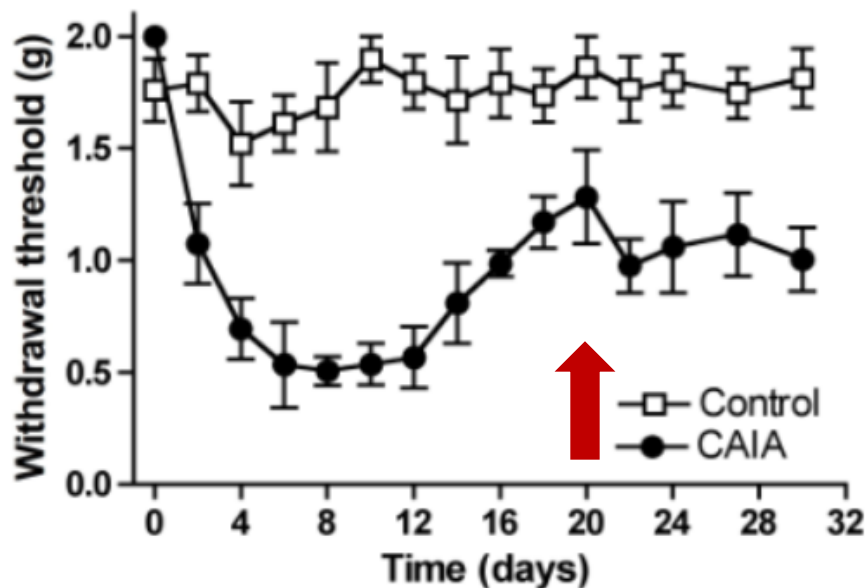
(Duygu Belkis Başı)

Arthritis symptoms



(pain hypersensitivity)

Pain, tactile allodynia



Collagen Antibody Induced Arthritis (CAIA) leads to persistent pain in mice even after cessation of inflammation on day 20

Method 2

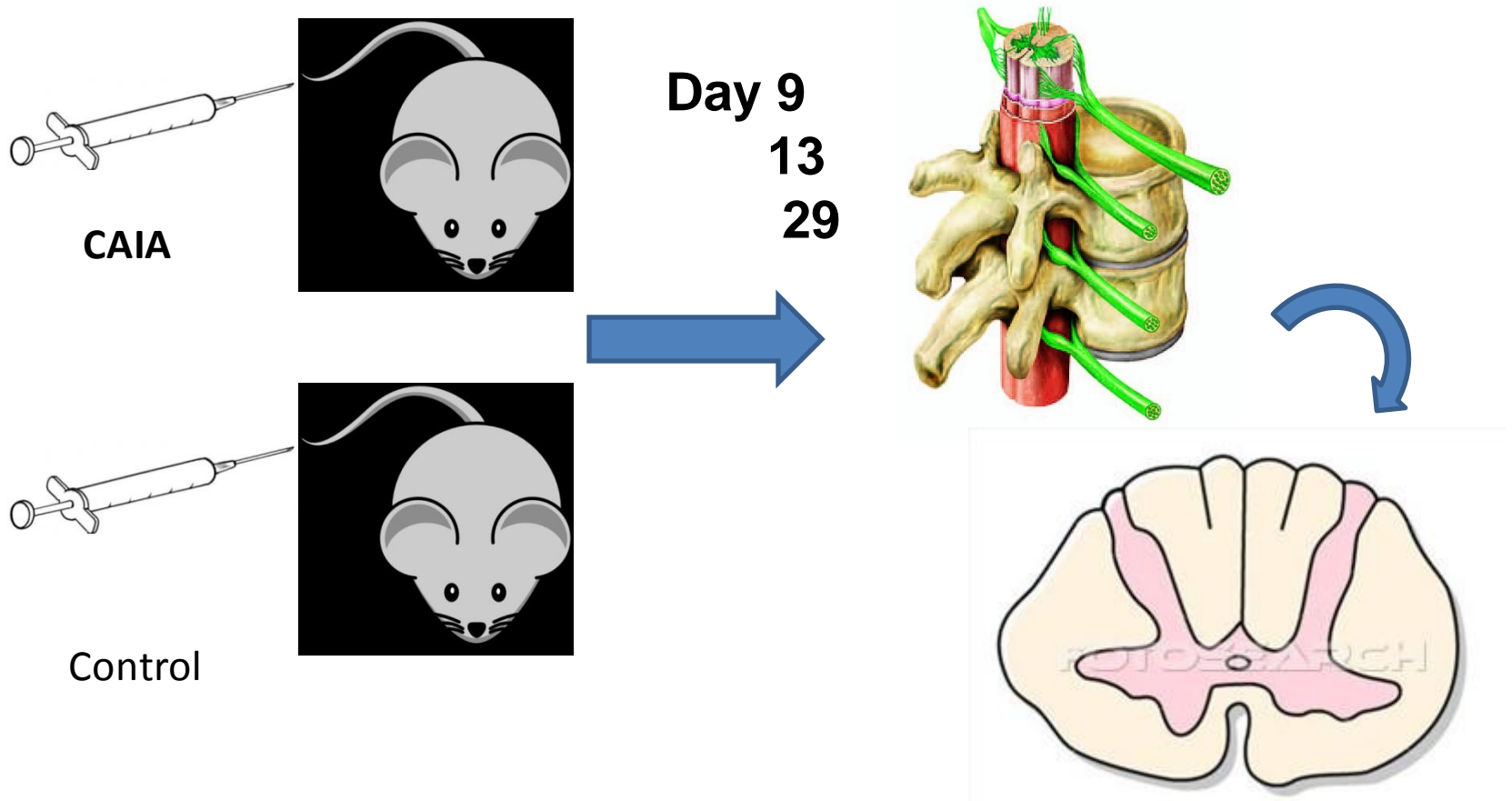


Image 1: Injection <<http://www.edupics.com/injection-t12187.jpg>> Web access date: 21 Aug 2010

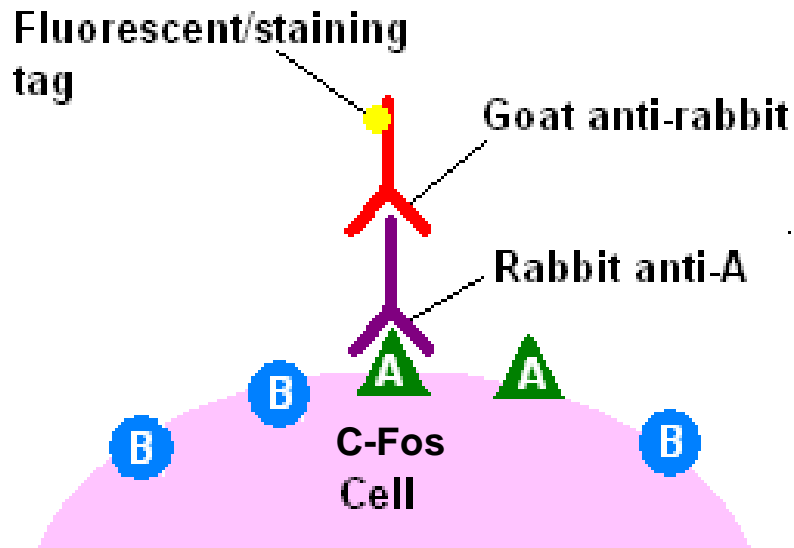
Image 2: Mouse <http://www.clker.com/cliparts/e/2/0/6/12154415421767612404lemmling_Simple_cartoon_mouse.svg.hi.png> Web access date: 21 Aug 2010

Image 3: Spinal cord: <http://www.dorlingkindersley-uk.co.uk/static/clipart/uk/dk/exp_humanbody/exp_human045.jpg> Web access date: 21 Aug 2010

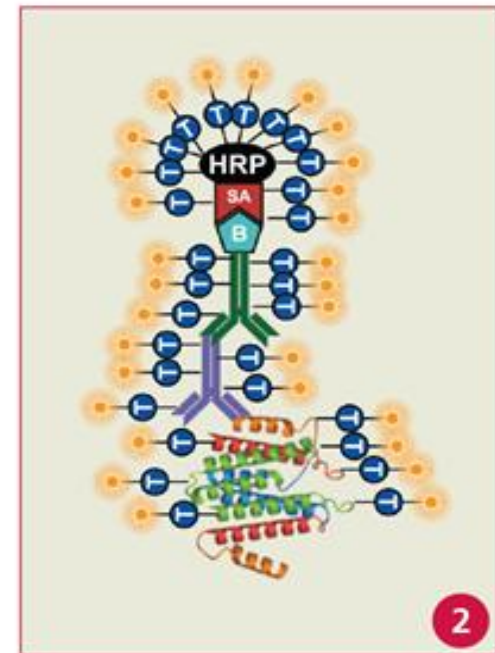
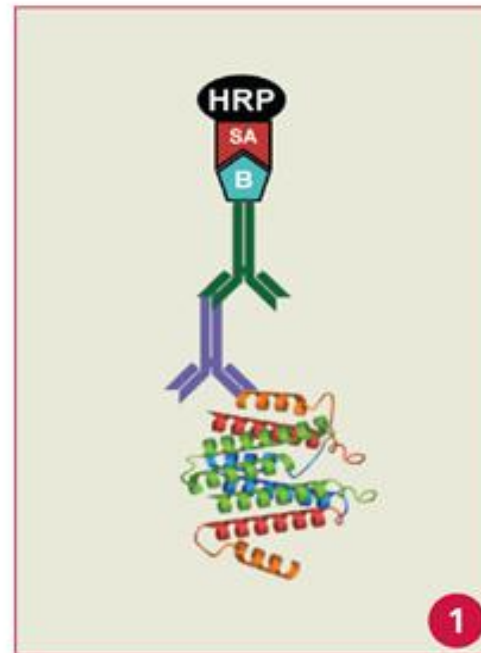
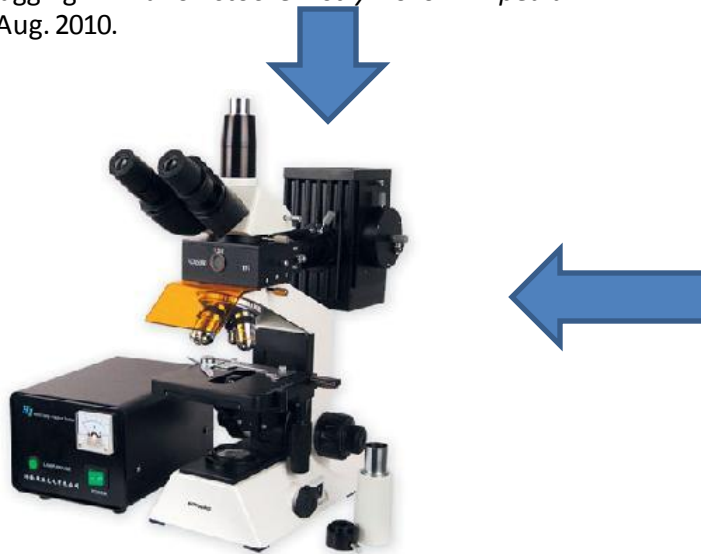
Image 4: Spinal slice cartoon: sa702067 <www.fotosearch.com> Web access date: 23 Aug 2010

Immunohistochemistry

Tyramide Signal Amplification

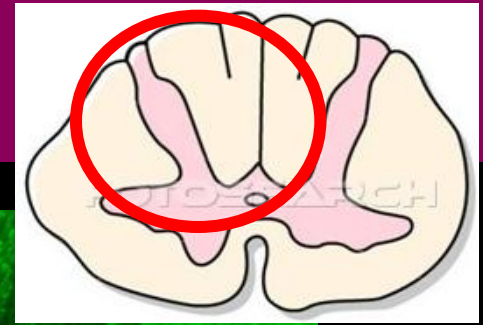


Indirect tagging. *Immunohistochemistry*. 2010. Wikipedia. Web. 16 Aug. 2010.



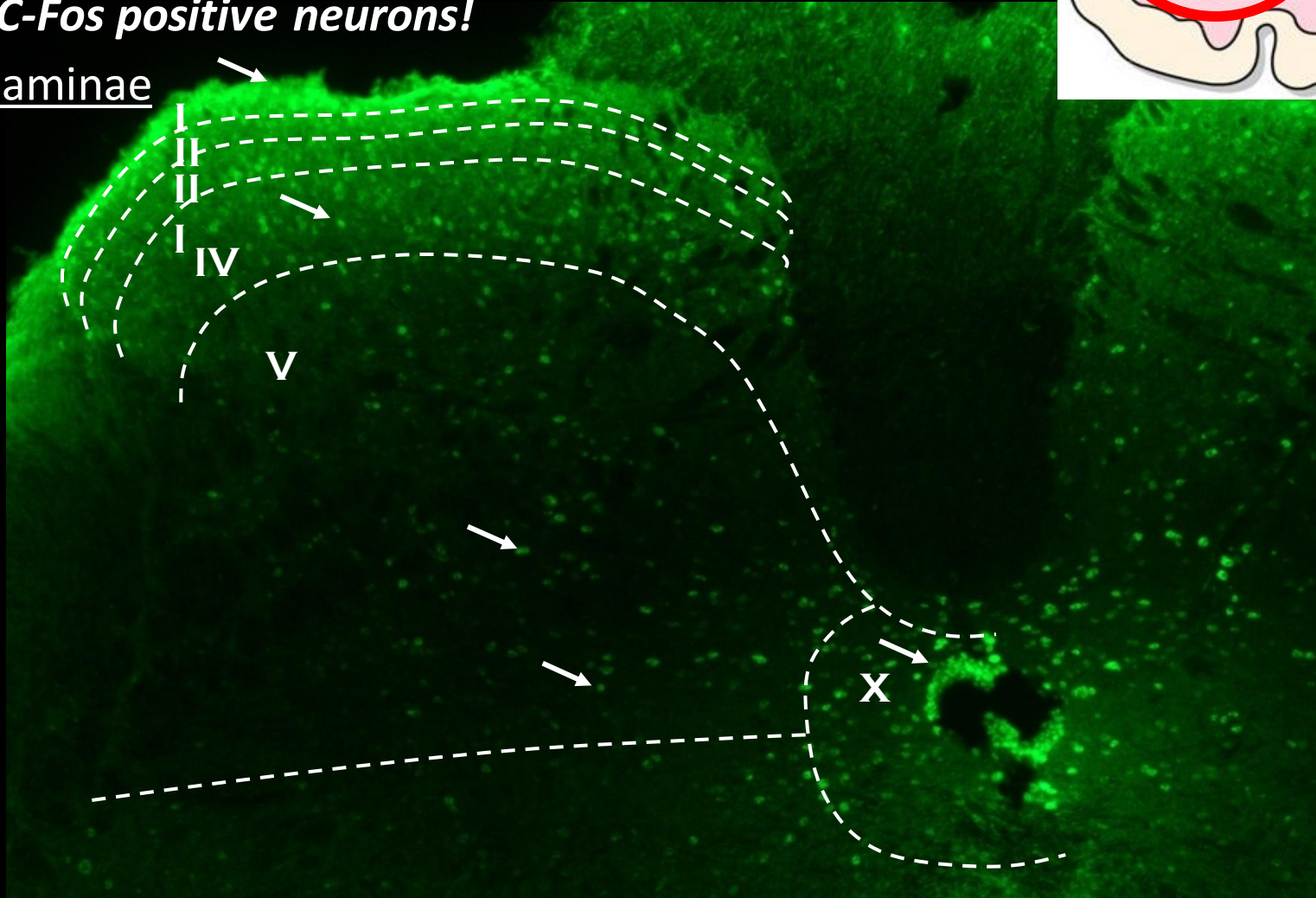
Tyramide Signal Amplification Systems. 2010. PerkinElmer. Web. 16 Aug. 2010.

Results c-Fos

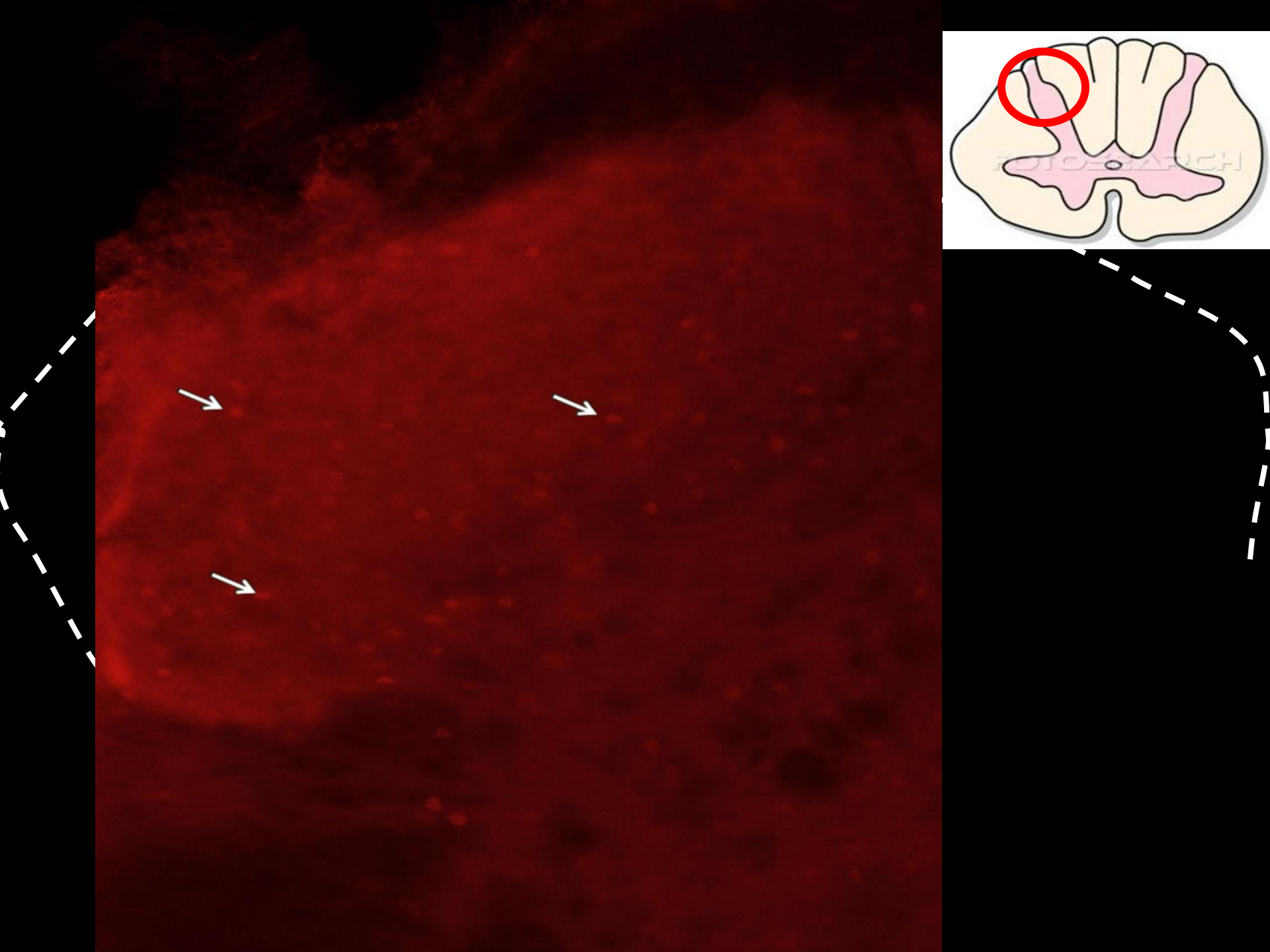
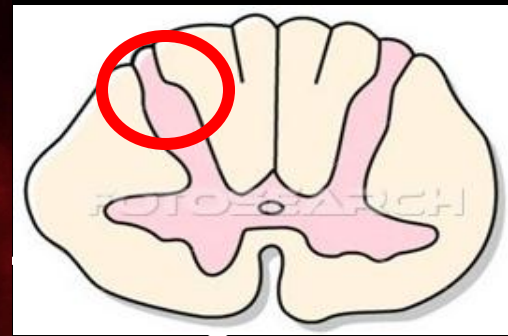


C-Fos positive neurons!

Rexed laminae

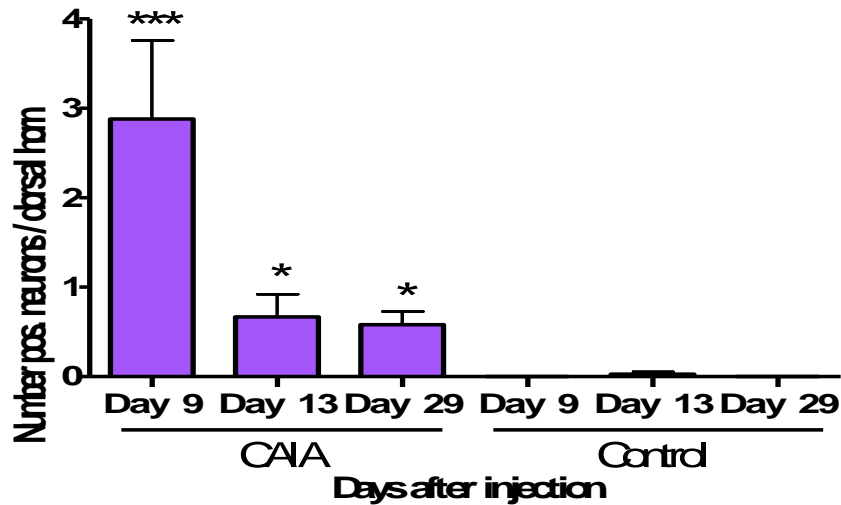


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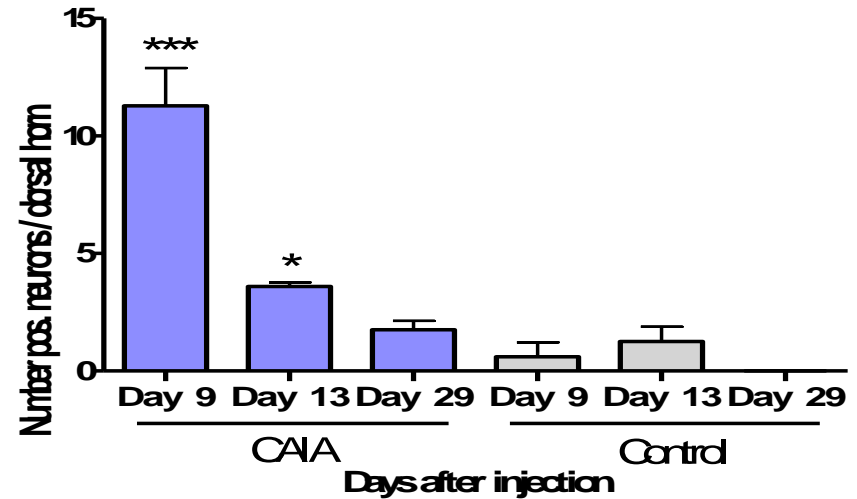


c-Fos expression in the spinal dorsal horn is elevated subsequent to induction of joint inflammation

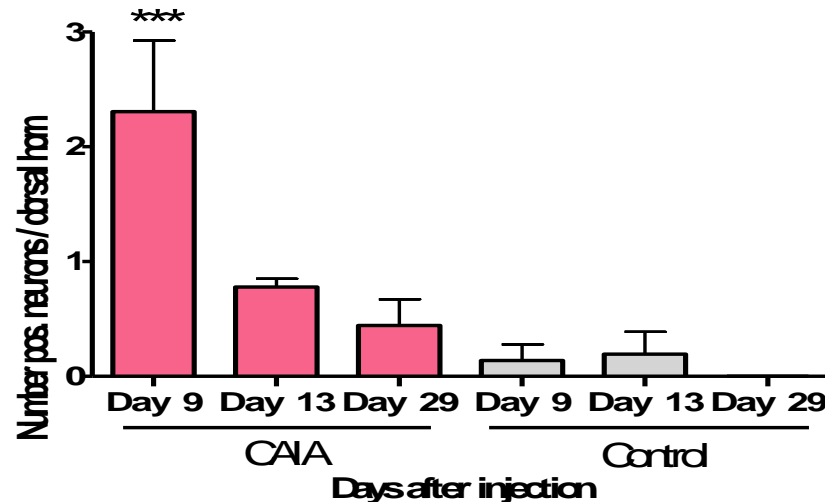
c-Fos laminae II



c-Fos laminae IV-V



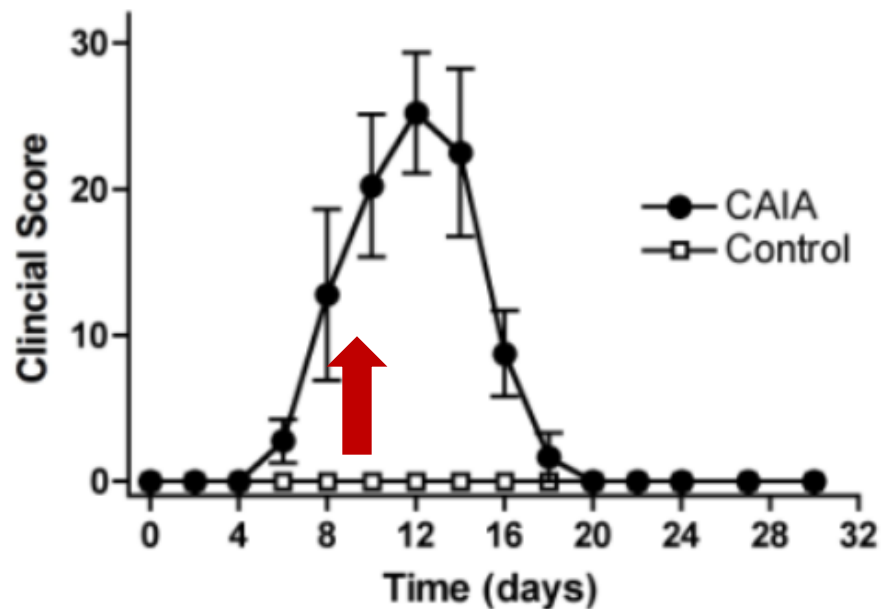
c-Fos lamina X



Results

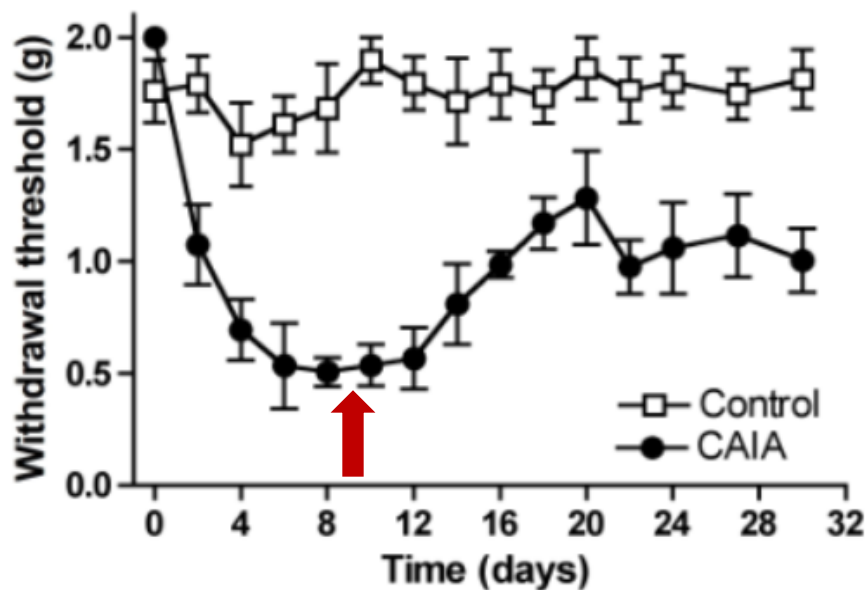
(Duygu Belkis Başı)

Arthritis symptoms



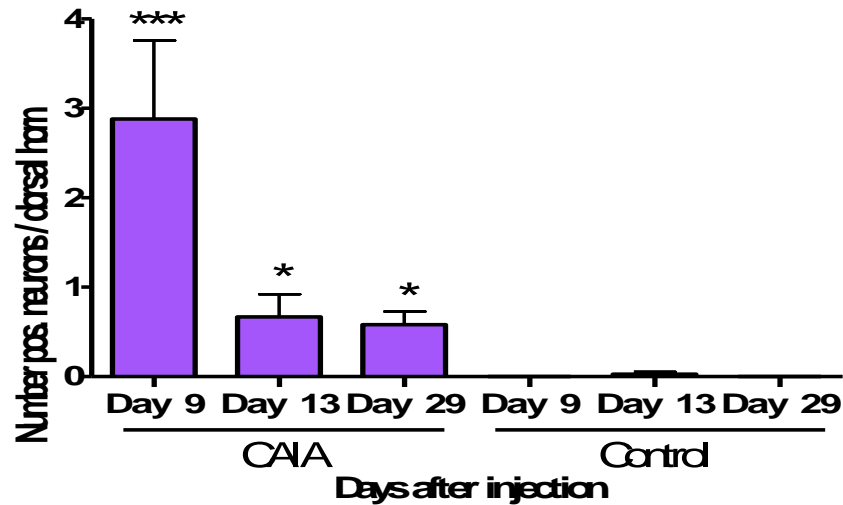
(pain hypersensitivity)

Pain, tactile allodynia

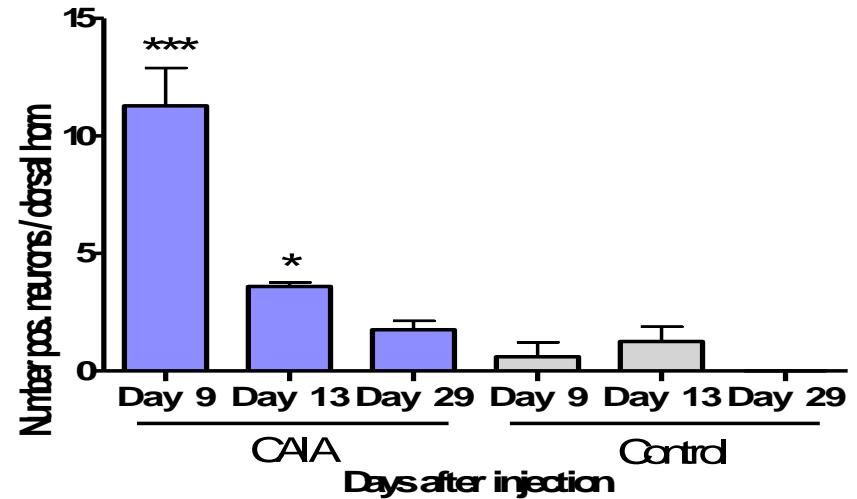


c-Fos expression in the spinal dorsal horn is elevated subsequent to induction of joint inflammation

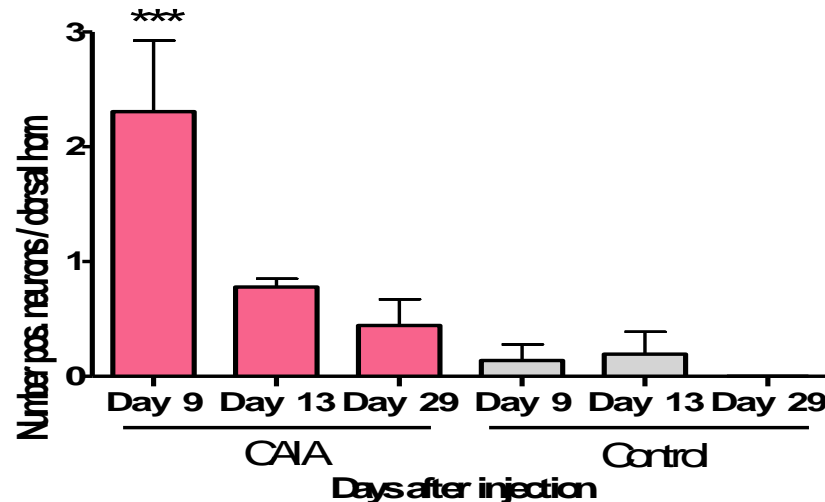
c-Fos laminae II



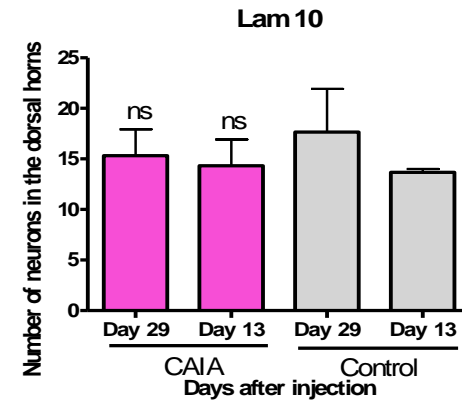
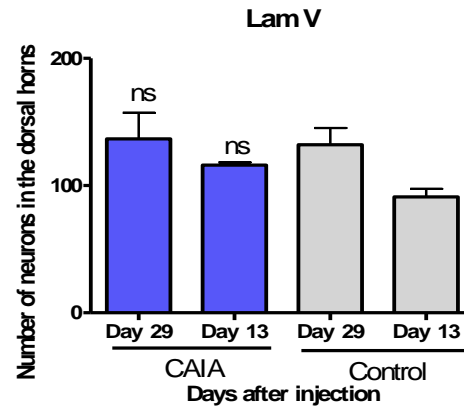
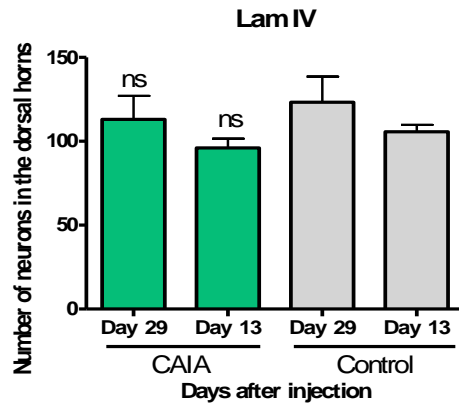
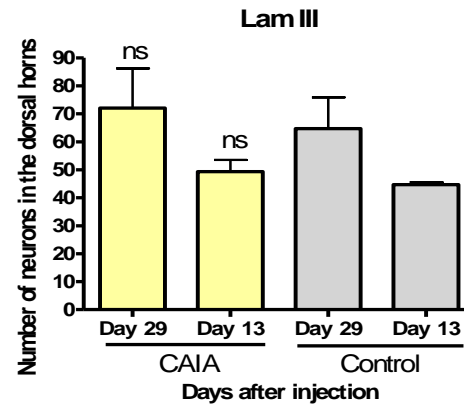
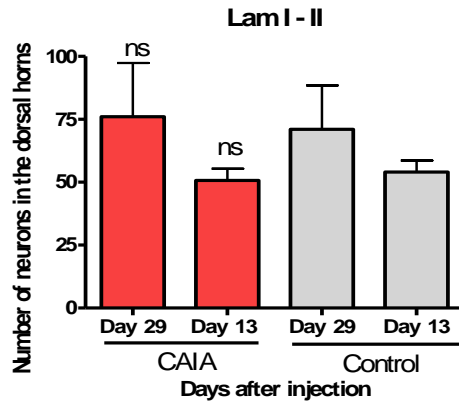
c-Fos laminae IV-V



c-Fos lamina X



Results ATF-3



Summary

- **Joint inflammation → increases c-Fos expression (=active neurons) in the spinal dorsal horn**

Most pronounced:

- on day 9 (inflammatory phase)

- **Allodynia (pain hypersensitivity) persists beyond the inflammatory phase**

- the number of c-Fos positive neurons is increased as compared to control mice on day 29

Summary

- **ATF-3: not significantly higher after CAIA induction**
- **Increase in both CAIA and control after the inflammation**
 - Accumulation after nerve injury
(possibly the act of the injection itself)

Thank you!



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