Cellular and molecular basis for shock wave application to the musculo-skeletal system

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Why listen to him?
(he is working in psychiatry...)

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Aim

Application of shock waves to the musculo-skeletal system:

- Tendinosis calcarea of the rotator cuff
- Epicondylitis lateralis humeri
- Plantar fasciitis
- Pseudarthrosis
- (other indications)

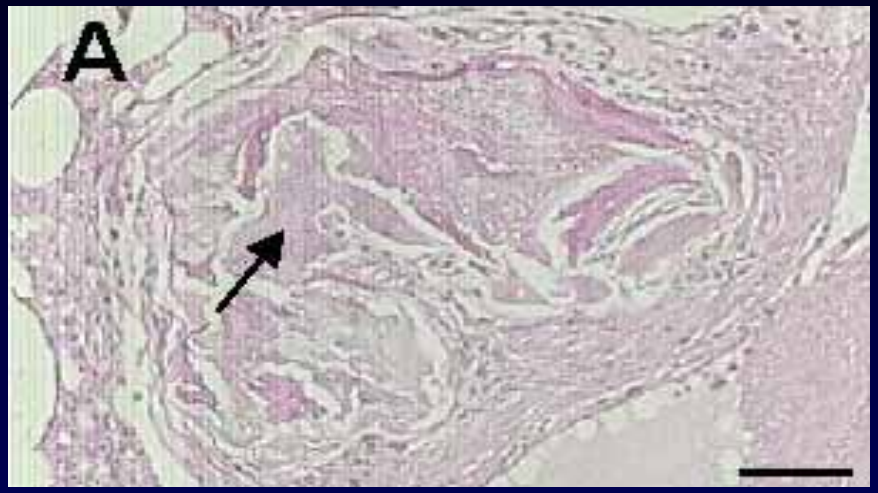
$\rightarrow$ Diagnosis-oriented application of shock waves

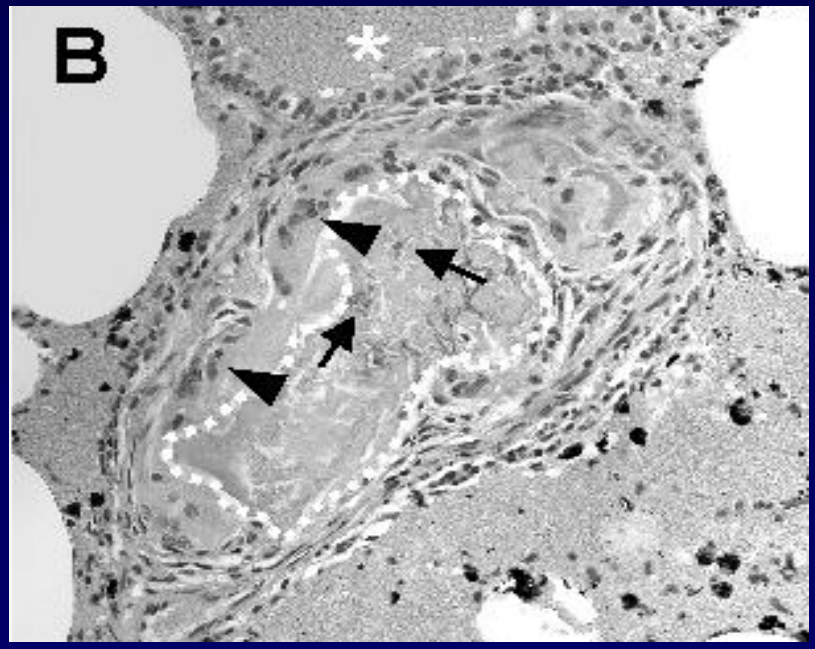
Approach

Criteria for the selection of proper settings/adjustments of parameters in diagnosis-oriented application of shock waves:

- Experience (empirical basis)
- Example: higher energy flux densities necessary in the treatment of plantar fasciitis than of epicondylitis lateralis humeri
- Avoidance of unwanted side effects (“nihil nocere”)

Unwanted side effects (example)





Knowledge (1)

Pro shock waves (pilot studies):

- Many reports (pilot studies) in the literature about sucessful application of shock waves in the treatment of tendinosis calcarea of the rotator cuff, epicondylitis lateralis humeri, plantar fasciitis, pseudarthrosis, etc.

Pro shock waves (prospective, randomized, controlled studies):

- Tendinosis calcarea of the rotator cuff (Gerdesmeyer et al., JAMA 2003)
- Plantar fasciitis of athletes (Rompe et al., Am J Sports Med 2003)
- Others

Knowledge (2)

Contra shock waves (prospective, randomized, controlled studies):

- Tendinosis calcarea of the rotator cuff (Speed et al., J Bone Joint Surg Br 2002)
- Epicondylitis lateralis humeri (Haake et al., J Bone Joint Surg Am 2002; Speed et al., J Orthop Res 2002; Melykan et al., J Bone Joint Surg Br 2003)
- Plantar fasciitis (Haake et al., BMJ 2003; Speed et al., J Orthop Res 2003)

Knowledge (3)

Lateral epicondylitis / tennis elbow:

"Extracorporeal shock wave treatment as applied in the present study was ineffective in the treatment of lateral epicondylitis."

Haake et al., J Bone Joint Surg AM: 84-A (2002) 1982-1991

Plantar fasciitis / chronic heel pain:

"We found no evidence to support a beneficial effect on pain, function, and quality of life of ultrasound guided ESWT over placebo in patients with ultrasound-proven plantar fasciitis 6 and 12 weeks following treatment."

Buchbinder et al., JAMA 288 (2002) 1364-1372

Calcifying tendinitis /tendinosis of the rotator cuff:

"[…] after moderate doses of ESWT in patients with non-calcific tendonitis of the rotator cuff, […] there is no evidence of added benefit when compared with sham treatment."

Speed et al., J Bone Joint Surg Br 84 (2002) 509-512

What are the reasons for this discrepancy?

Specific problem (1)

Special (i.e., diagnosis-oriented therapeutic aims of shock wave application

Example: treatment of tendinosis calcarea of the rotator cuff with shock waves

- Disintegration of the depots (?)
- Remission of the inflammatory reaction (?)
- Long-term analgesia (?)
- Combination of these therapeutic aims – priorities (?)
- Consideration of individual predisposition (individual use of the shoulder; individual anatomy of the shoulder joint [MRI] (?)

Potential solution (1)

Special (i.e., diagnosis-oriented) mechanisms of action of shock waves

Example: induction of long-term analgesia in the treatment of tendinosis calcarea of the rotator cuff

- By disintegration of the depots - mechanical action of shock waves (?)
- By remission of the inflammatory reaction – biochemical mediation of shock wave action (?)
- By inhibition of spinal transduction of afferences by short-term hyperstimulation – neurophysiologic action of shock waves (?)
- Other mechanisms (?)
- Combination of these mechanisms (?)

Potential solution (2)

Setting criteria for the application of shock waves

- Not primarily in relation to a certain diagnosis, but
- rather in relation to mechanisms of action of shock waves on the musculo-skeletal system

Mechanisms of action (1)

Known (K) and hypothesized (H) mechanisms of action of shock wave application

- Induction of action potentials in peripheral nerves (**K**; Schelling et al., Biophys J 1994)
- Release of substance P in periost (**K**; Maier et al., Clin Orthop 2003)
- Reduction in expression of CGRP (calcitonin gene-related peptide) in spinal ganglia (**K**; Takahashi et al., Auton Neurosci 2003)
- Inhibition of spinal transduction of afferences by short-term hyperstimulation (Melzack) (**H**)

Mechanisms of action (2)

Known (K) and hypothesized (H) mechanisms of action of shock wave application

- Alterations in the histologic composition of soft tissue (**K;** e.g. Achilles tendon; Rompe et al., J Bone Joint Surg Br 1998; quadriceps tendon; Maier et al., Arch Orthop Trauma Surg 2002)
- Induction of new bone formation (**K;** Tischer et al., Z Orthop Ihre Grenzgeb 2002; Wang et al., Bone 2004)
- Induction of vasculogenesis (formation of new vessels) (**K;** Wang et al., J Orthop Res 2003)
- Activation/recruitment of mesenchymal stem cells (**K;** Wang et al., J Orthop Res 2004)

Mechanisms of action (3)

Known (K) and hypothesized (H) mechanisms of action of shock wave application

- Induction of bone fractures (**K;** e.g. Delius et al., Ultrasound Med Biol 1995)
- Selective destruction of non-myelinated nerve fibers (**K;** Maier et al., unpublished results)

Shock wave triggering

New interpretation of known and hypothesized mechanisms of action of shock wave application

- Induction von action potentials in peripheral nerves
- Release of substance P in periost
- Reduction in expression of CGRP (calcitonin gene-related peptide) in spinal ganglia
- Inhibition of spinal transduction of afferences by short-term hyperstimulation

→ in a broader sense: “triggering”

Shock wave tissue engineering

New interpretation of known and hypothesized mechanisms of action of shock wave application

- Alterations in the histologic composition of soft tissue
- Induction of new bone formation
- Induction of vasculogenesis (formation of new vessels)
- Activation/recruitment of mesenchymal stem cells

$\rightarrow$ in a broader sense: “tissue engineering”

Shock wave surgery

New interpretation of known and hypothesized mechanisms of action of shock wave application

- Induction of bone fractures
- Selective destruction of non-myelinated nerve fibers

$\rightarrow$ in a broader sense: “surgery”

Therapeutic aims - triggering

Mechanisms of action of shock waves:

Shock wave triggering

- Low energy flux densities
- Field of action of radial shock waves

Therapeutic aim: stimulation of the peripheral and central nervous system in order to cause different effects on the musculo-skeletal system

Therapeutic aims (2)

Mechanisms of action of shock waves:

Shock wave tissue engineering

- Medium energy flux densities
- Radial and focused shock waves

Therapeutic aim: alterations in the histologic composition of soft tissue (tendons, vessels), with indirect effects on bone

Therapeutic aims (3)

Mechanisms of action of shock waves:

Shock wave surgery

- High energy flux densities
- Focused shock waves
- Use of shock wave devices that are currently not in clinical use

Therapeutic aim: destruction of tissue

Examples in a new look (1)

Possible application of shock waves oriented in relation to mechanisms of action

Example: treatment of tendinosis calcarea of the rotator cuff with shock waves

- Disintegration of the depots ⇒ surgery and/or triggering
- Remission of the inflammatory reaction ⇒ triggering
- Long-term analgesia ⇒ triggering / surgery (ultima ratio)

Examples in a new look (2)

Possible application of shock waves oriented in relation to mechanisms of action

Example: treatment of plantar fasciitis with shock waves

- Disintegration of the calcaneal spur (if present) ⇒ surgery and/or triggering
- Remission of the inflammatory reaction ⇒ triggering
- Long-term analgesia ⇒ triggering / surgery (ultima ratio)

Need (1)

Novel orientation of basic research with respect to shock waves

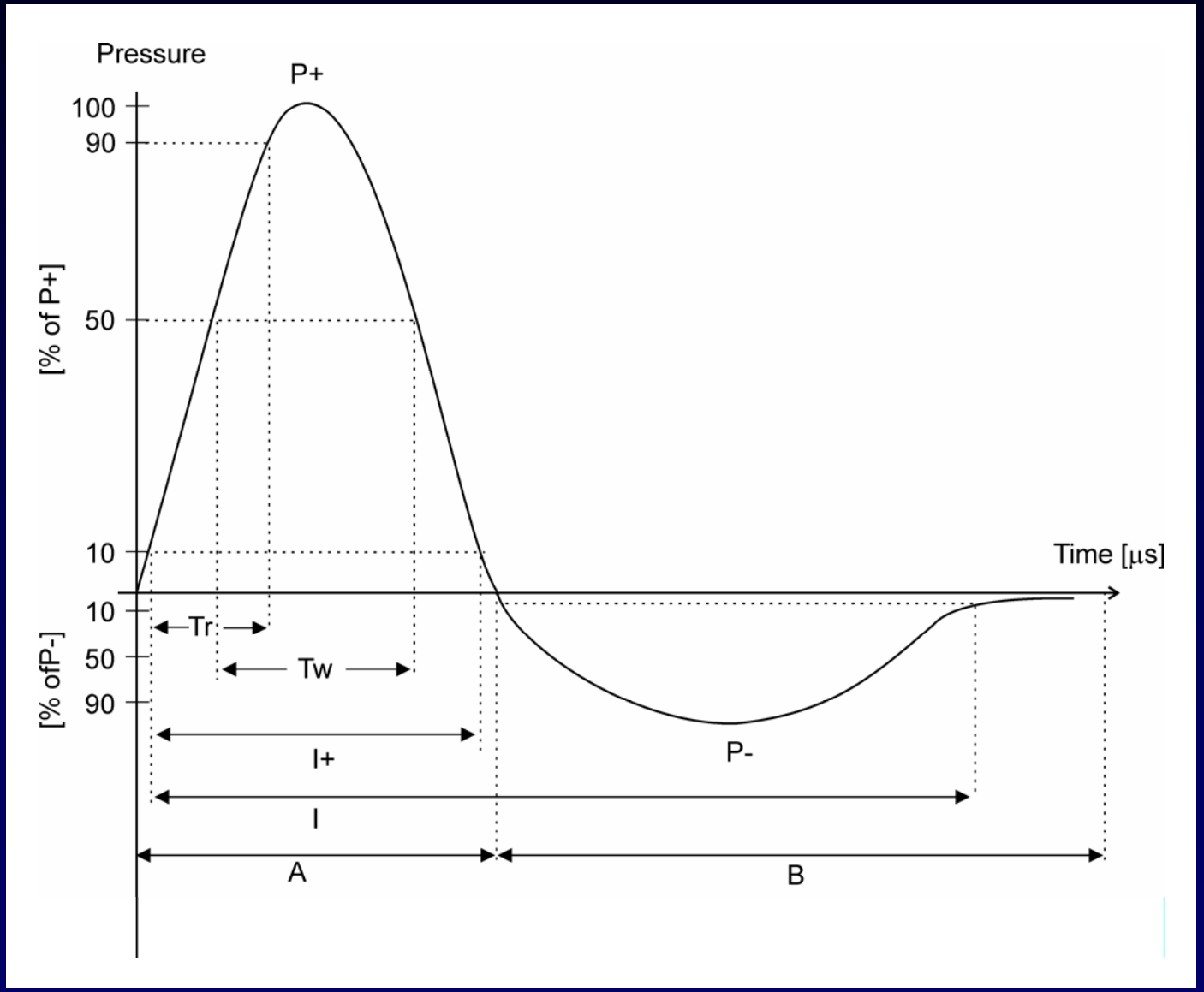
- First aim: more insights into the molecular and cellular mechanisms of action of shock waves on the musculo-skeletal system
- Second aim: activation of these mechanisms of action in relevant animal models of the corresponding diseases

Need (2)

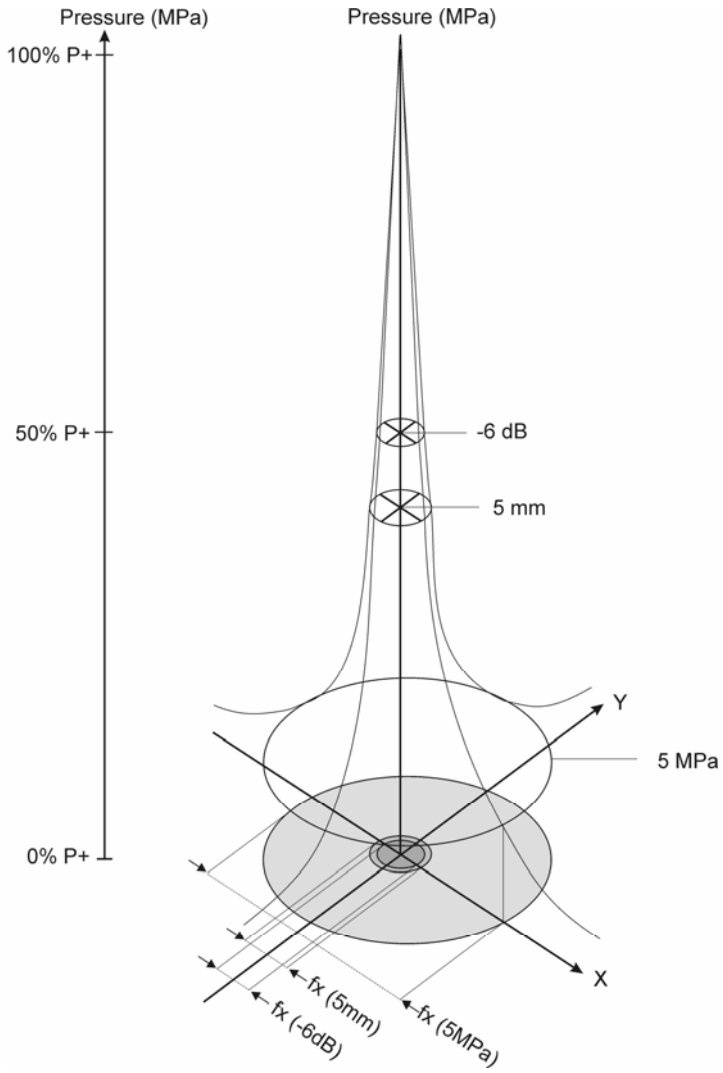
Novel focus in clinical applications (and clinical pilot studies, respectively) concerning shock wave application:

- Search for the activation of known and relevant mechanisms of action of shock waves in the treatment of the corresponding diseases
- Consideration of the individual predisposition of the patient (i.e., individual use of triggering, tissue engineering and surgery on different patients with the same diagnosis)
- Better knowledge of the molecular and cellular mechanisms of action of shock waves

Shock wave (1)



Shock wave (2)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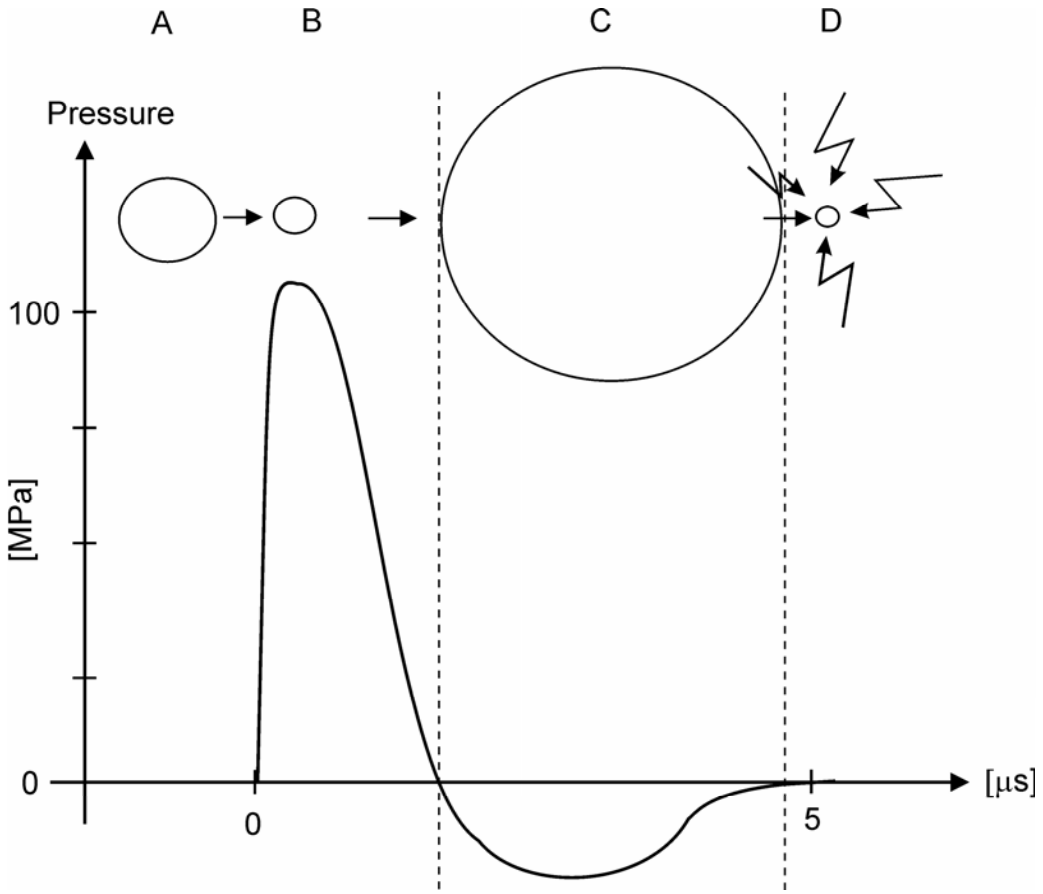
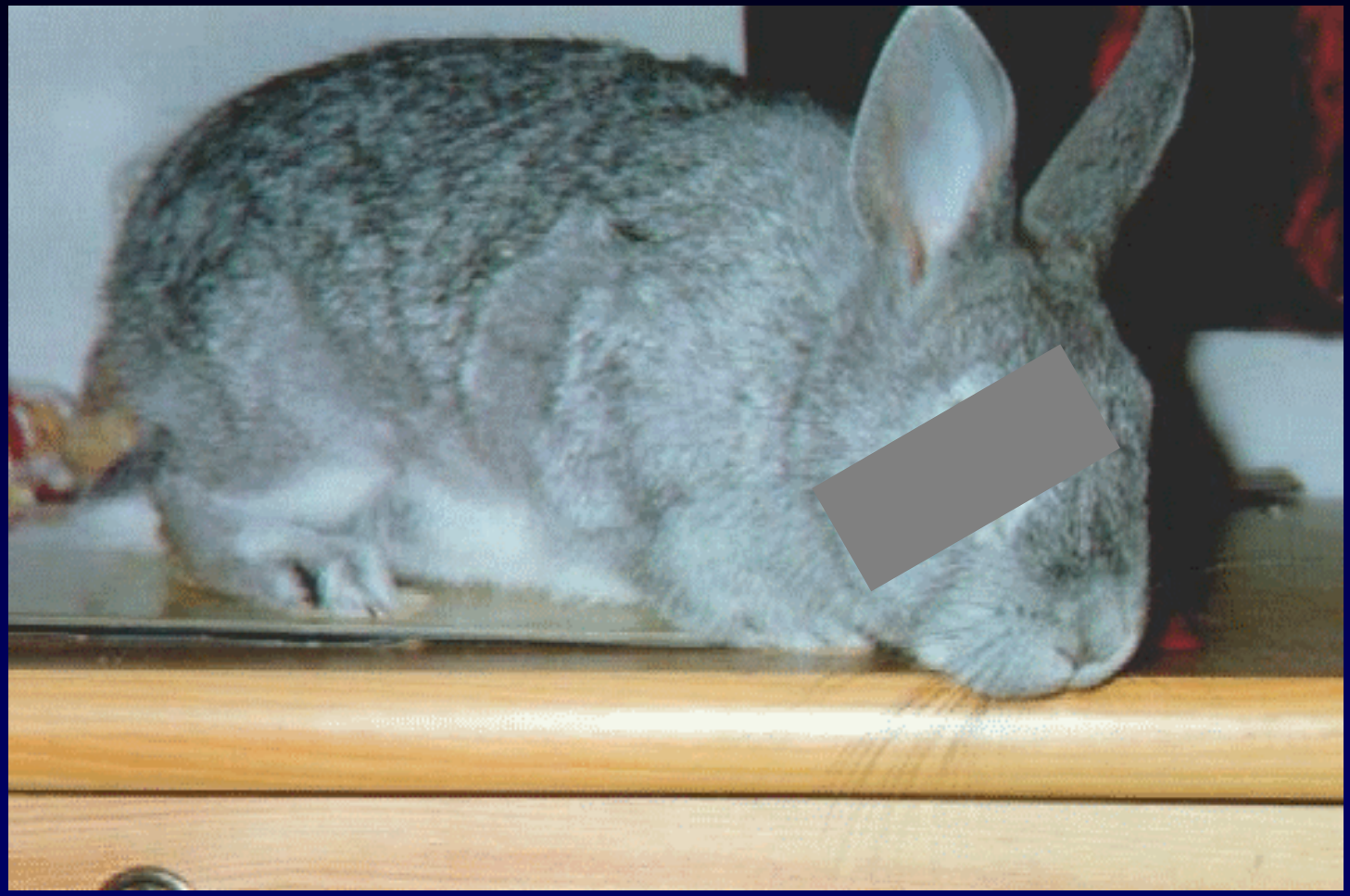
Shock wave (3)





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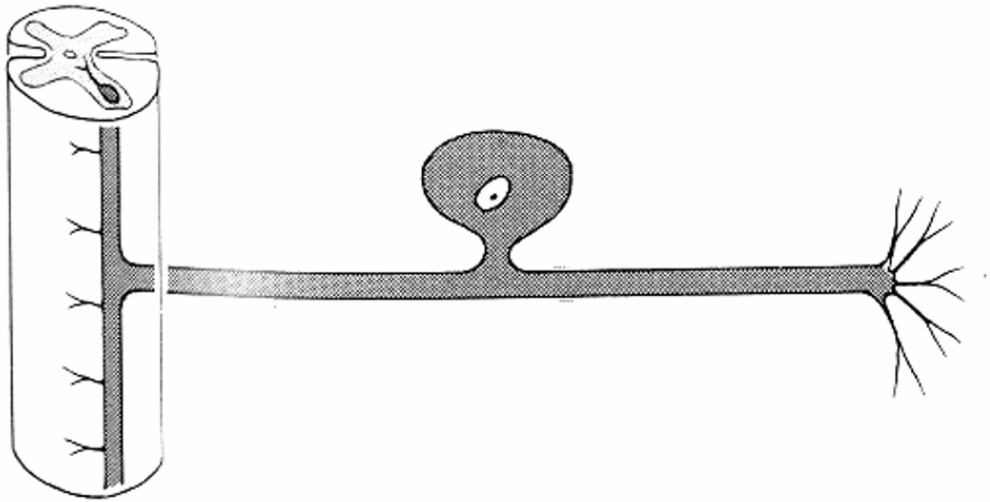

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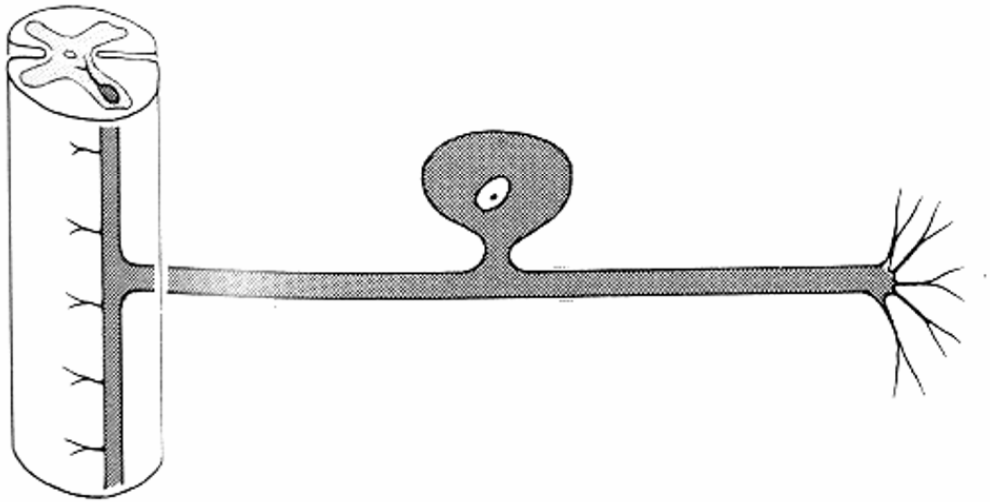
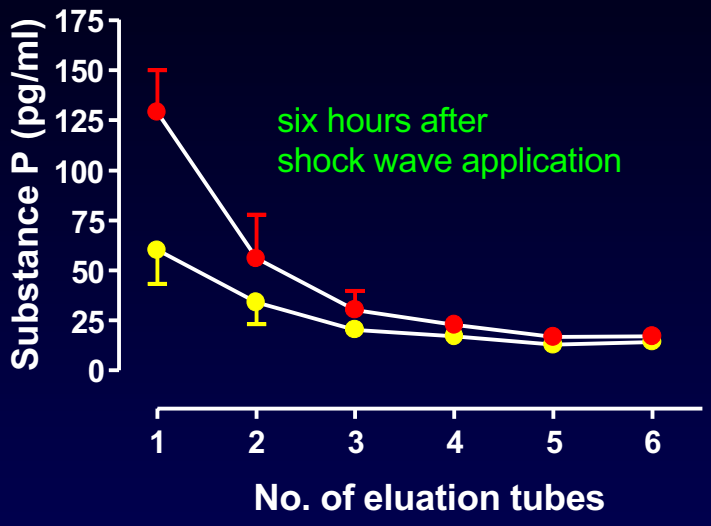
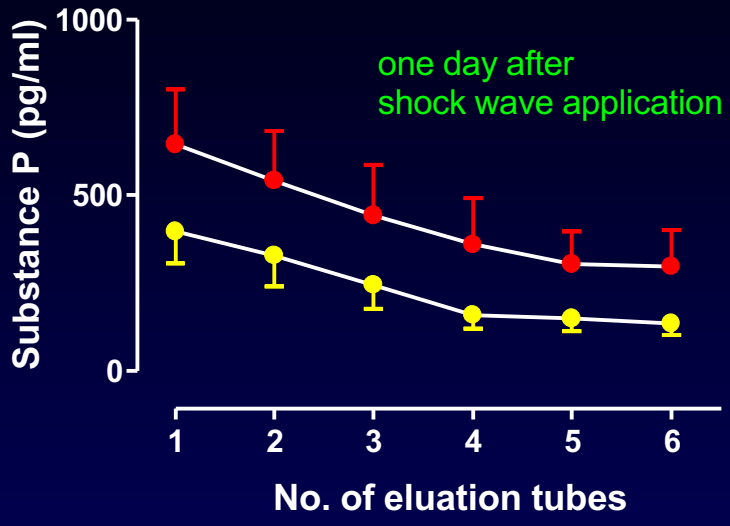


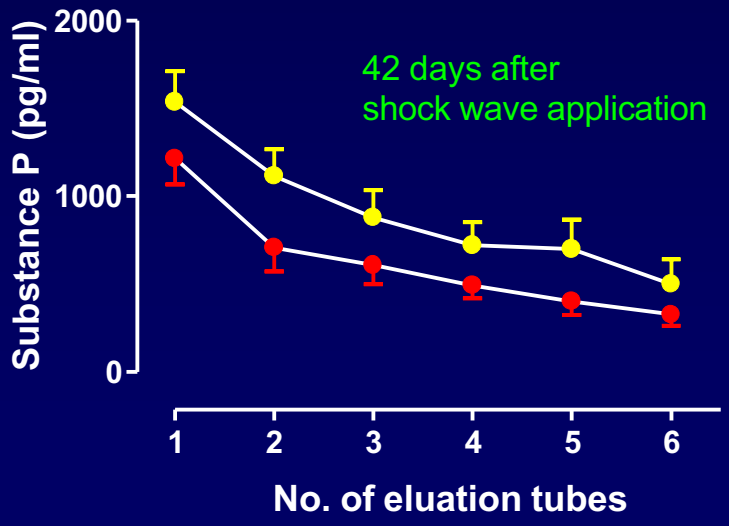
Study design (1)

- Rabbits (n=20)
- Application of extracorporeal shock waves *in vivo* to the right distal femur (energy flux density = 0.9 mJ/mm^2; 1,500 pulses at 1 / second)
- Analysis after
  - six hours (n=4),
  - one day (n=8), and
  - 42 days (n=8)
- Detection of substance P and prostaglandine E2 in the periost

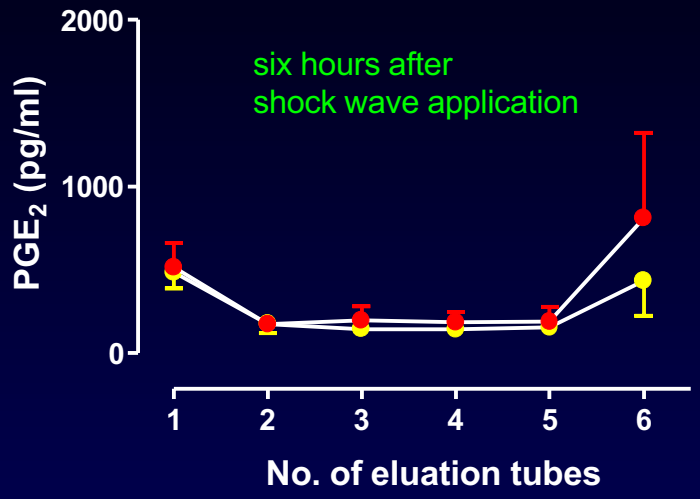
Results (1) – substance P

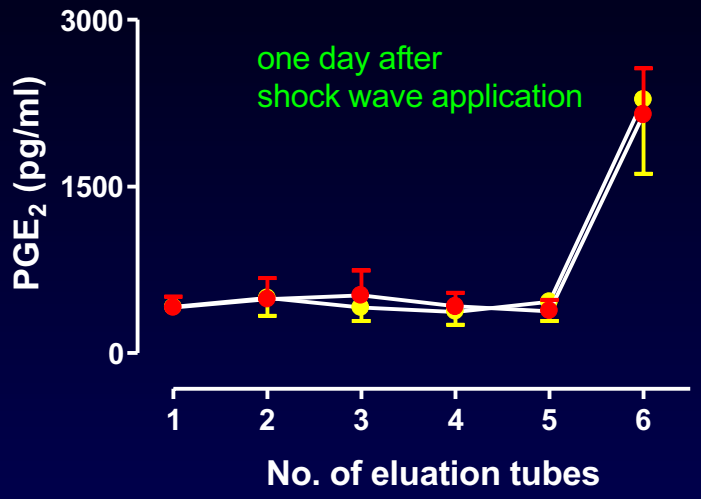


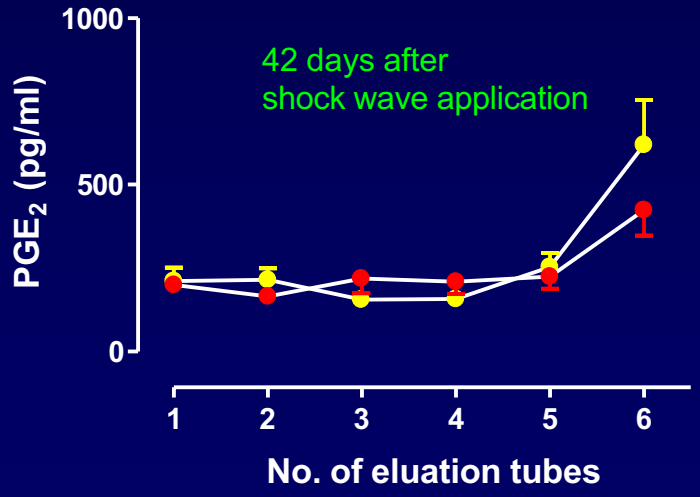




Results (1) – prostaglandine E2





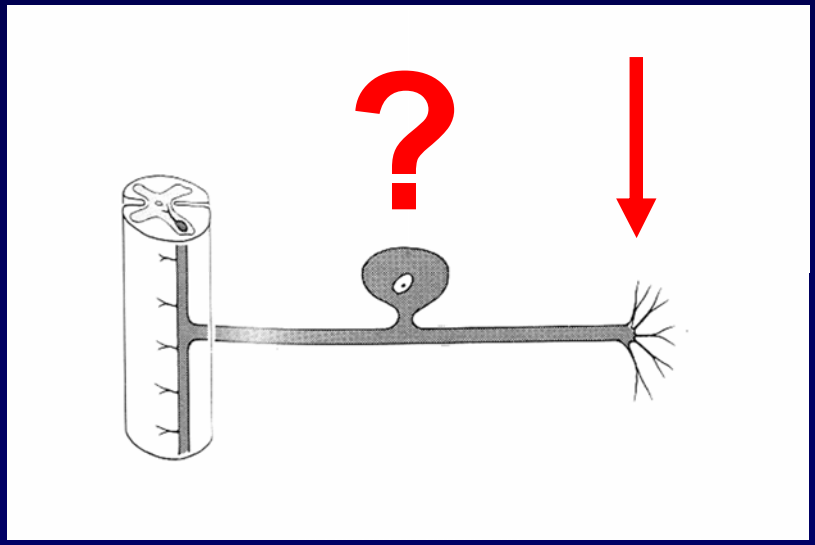


Clinical Orthopaedics and Related Research 2003; 406:237-245

Substance P and Prostaglandin E_2 Release After Shock Wave Application to the Rabbit Femur

Markus Maier, MD [*,**]; Beate Averbeck, PhD [†]; Stefan Milz, MD [‡]; Hans Jürgen Refior, MD [*]; Christoph Schmitz, MD [§]

The biologic action of extracorporeal shock wave application on the musculoskeletal system is poorly understood. To prove the hypothesis that alterations of tissue concentrations of substance P and prostaglandin E_2 are involved in the biologic action of shock waves, extracorporeal shock waves with energy flux density of 0.9 mJ/mm2 (1500 pulses at 1/second) were applied in vivo to the distal femur of rabbits. The concentrations of substance P and prostaglandin E_2 eluted from the periosteum of the femur were measured. Compared with the untreated contralateral hindlimbs, substance P release from the periosteum from the femur was increased 6 hours and 24 hours after extracorporeal shock wave application, but was decreased 6 weeks after extracorporeal shock wave application. By contrast, extracorporeal shock wave application did not result in altered prostaglandin E_2 release from the periosteum from the femur. Remarkably, there was a close relationship between the time course of substance P release found here, and the well-known clinical time course of initial pain occurrence and subsequent pain relief after extracorporeal shock wave application to tendon diseases. Accordingly, substance P might be involved in the biologic action of extracorporeal shock wave application on tissue of the musculoskeletal system. This is the first study providing insights into the molecular mechanisms of extracorporeal shock wave application to the musculoskeletal system.



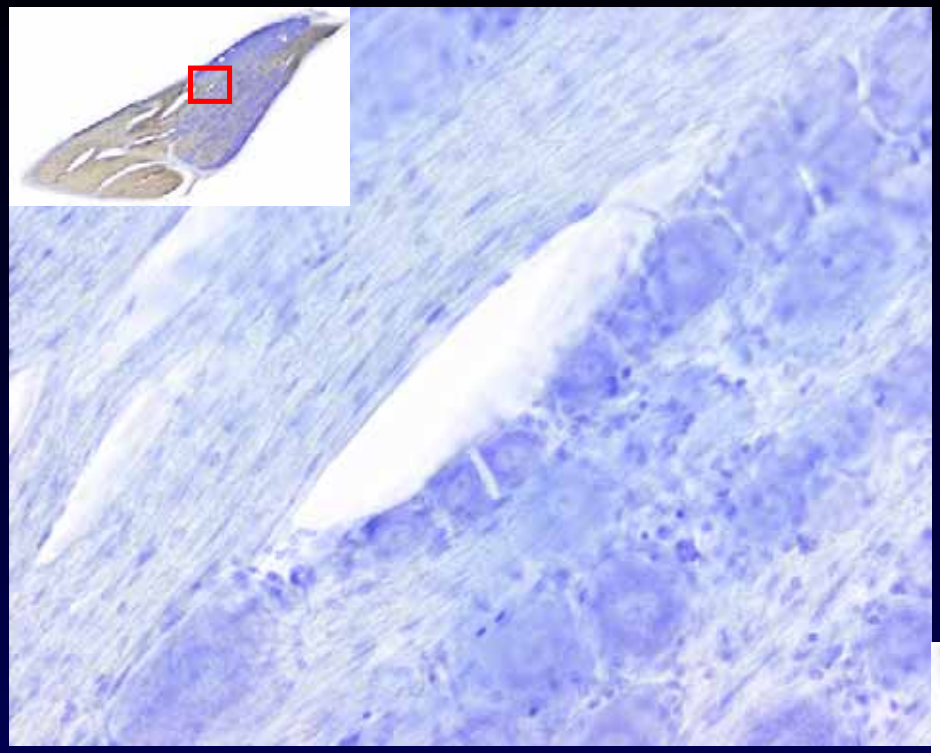
Study design (2)

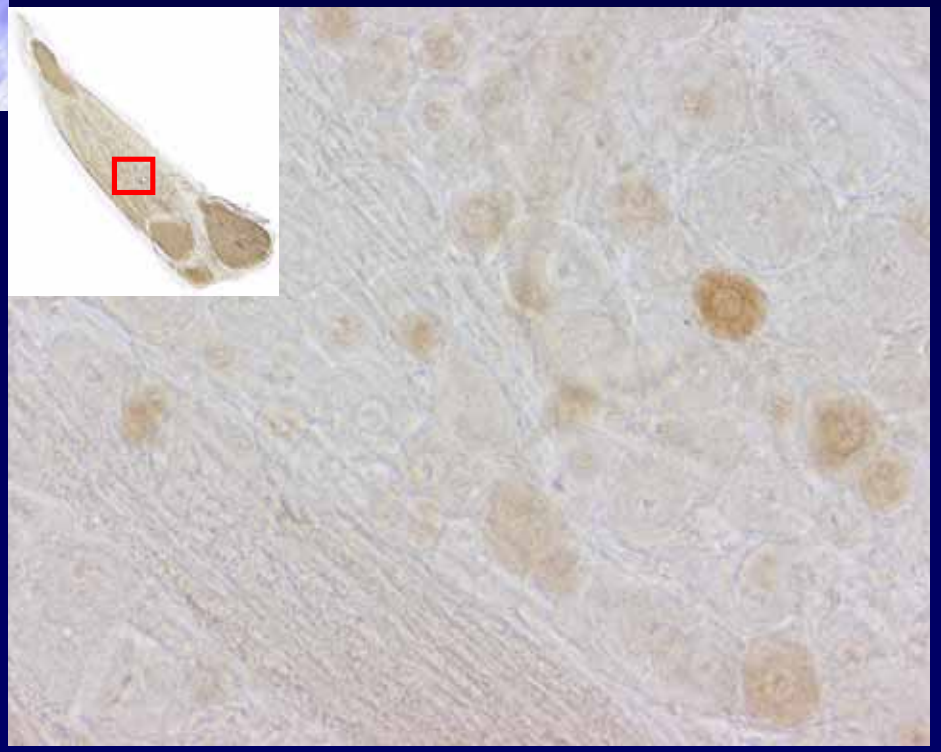
- Rabbits (n = 8)
- Application of extracorporeal shock waves *in vivo* to the right distal femur (energy flux density = 0.9 mJ/mm^2; 1500 pulses at 1 / second)
- After six weeks: analysis of the spinal ganglia L5, L6 and L7 with LM state-of-the-art morphometry (design-based stereology)

$\Rightarrow$ Total number of spinal ganglia neurons

$\Rightarrow$ Number of spinal ganglia neurons immunopositive for Substance P (i.e., expressing Substance P)

Cresyl-violet Substance P





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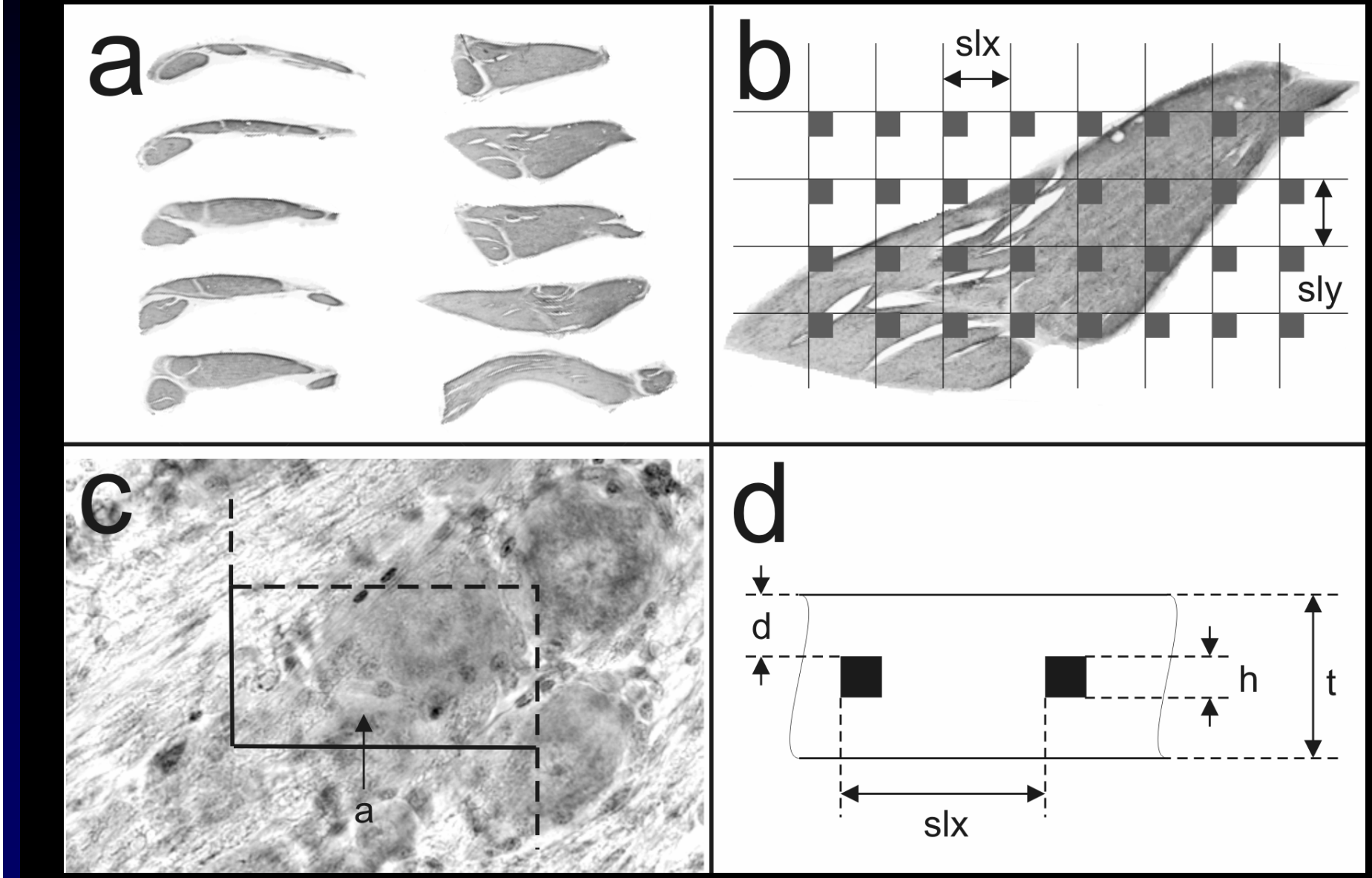
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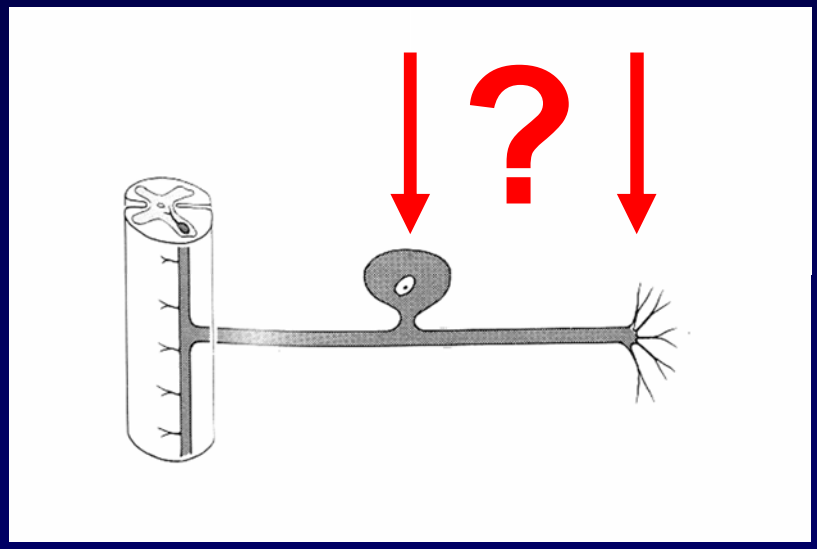
Corresponding alterations of Substance P expression (spinal ganglia) and availability (periphery) following extracorporeal shock wave application to the distal rabbit femur (EFD = 0.9 mJ/mm^2, 1500 pulses at 1 / second)



Study design (3)

- Rabbits (n = 8)
- Application of extracorporeal shock waves *in vivo* to the right distal femur (energy flux density = 0.9 mJ/mm^2; 1500 pulses at 1 / second)
- After six weeks: analysis of the femoral and sciatic nerves with state-of-the-art EM morphometry (design-based stereology)

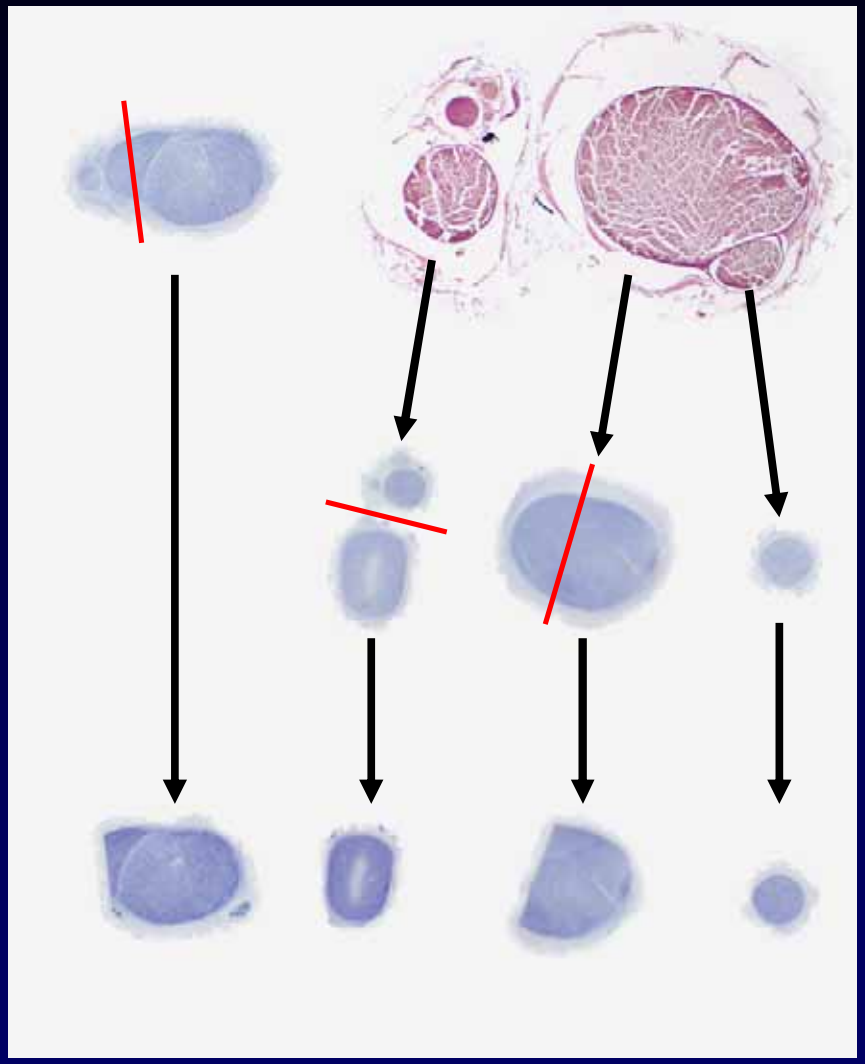
$\Rightarrow$ Cross-sectional areas of nerves

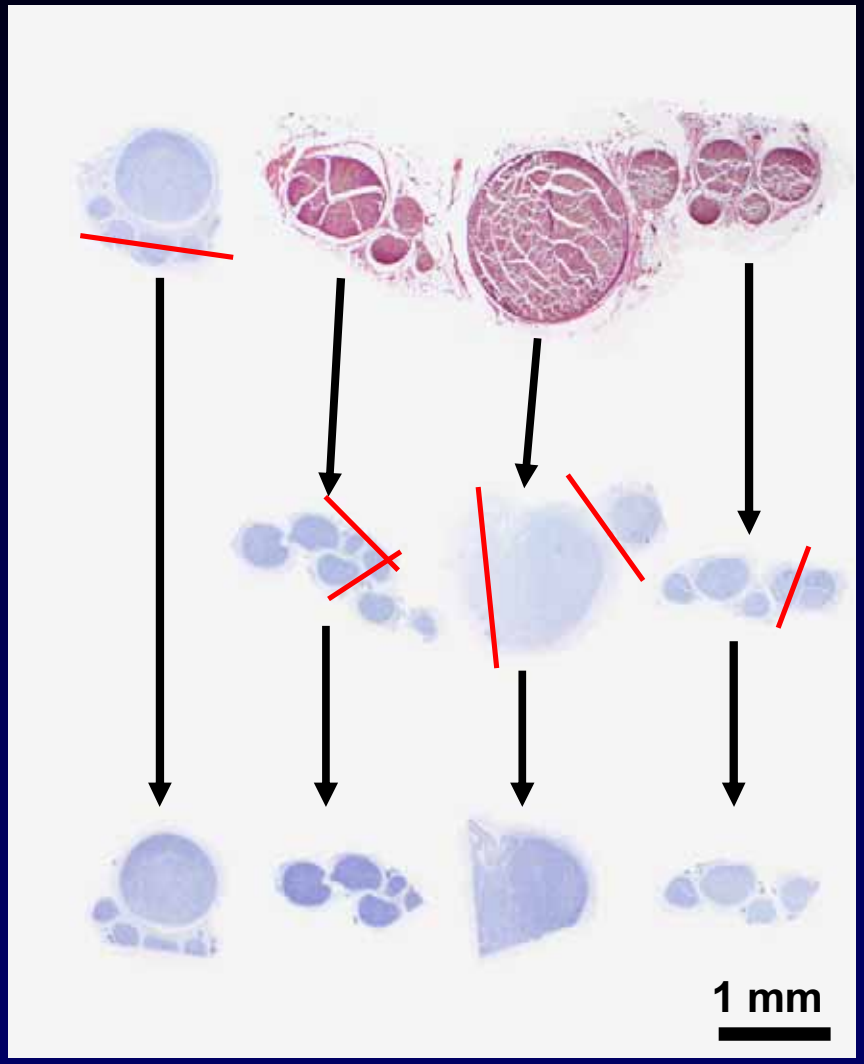
$\Rightarrow$ Densities of myelinated (large and small) and non-myelinated fibers

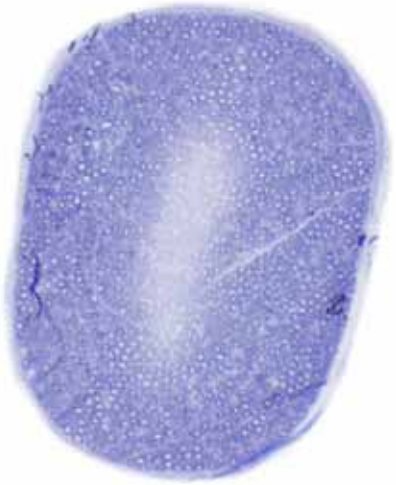
$\Rightarrow$ Numbers of myelinated (large and small) and non-myelinated fibers

left

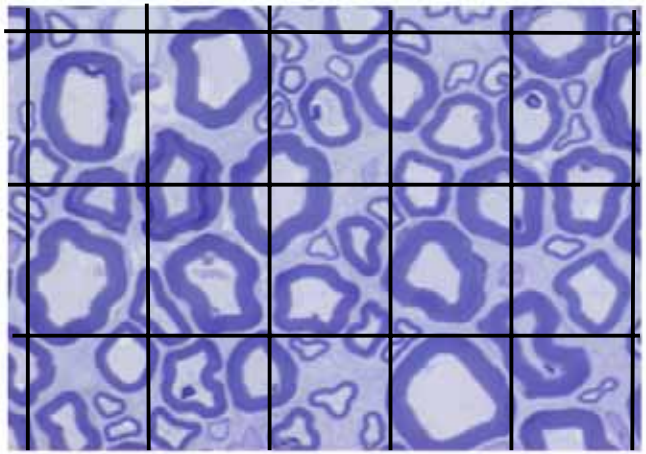
right



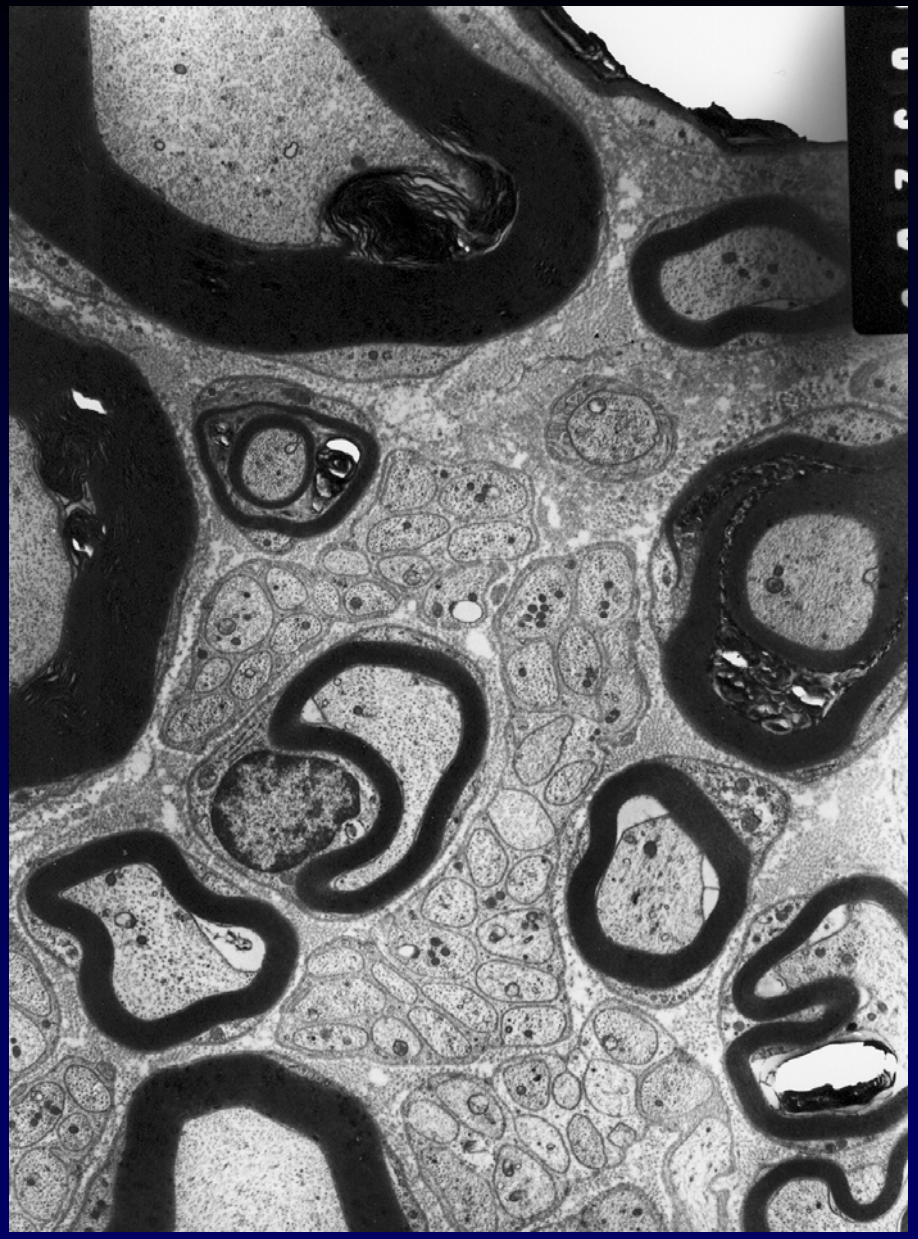




250 µm



25 µm



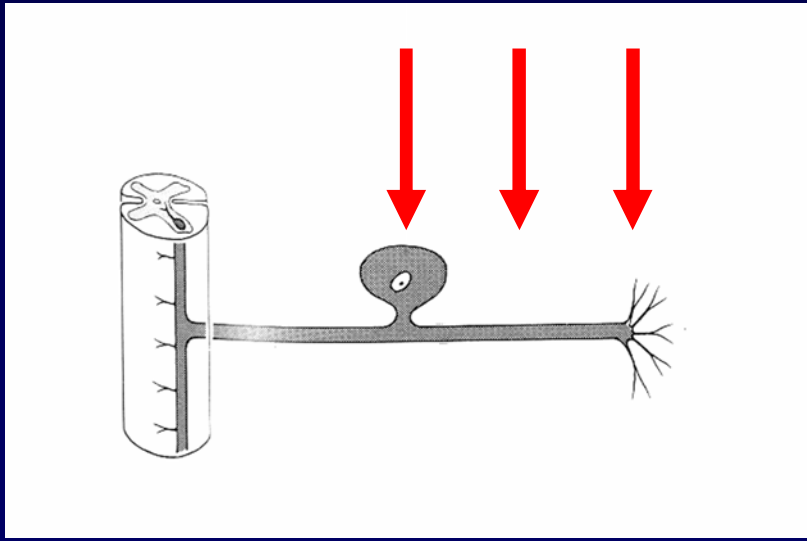
2 µm

Sciatic nerve

Femoral nerve

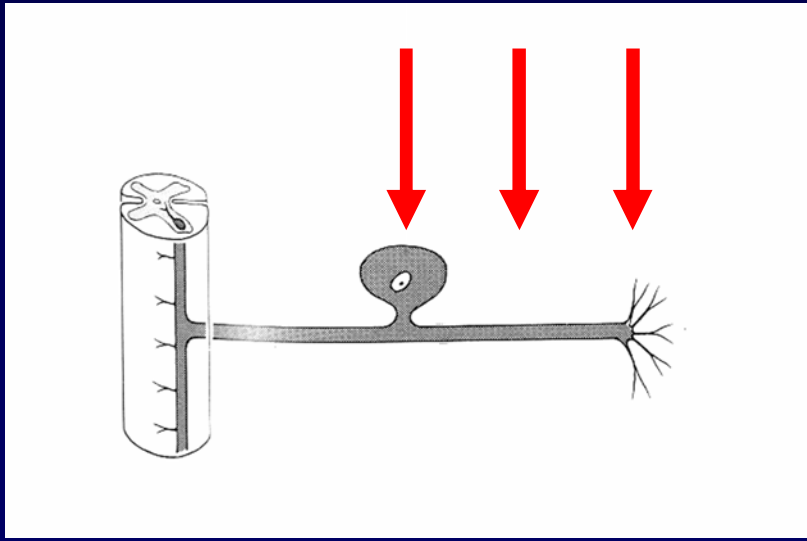
New hypothesis (1)

Extracorporeal shock wave application might (at least in part) act by partial denervation on the musculo-skeletal system



New hypothesis (2)

Extracorporeal shock wave application to the musculo-skeletal system might be an alternative to surgical treatments rather than to conservative approaches



Outlook

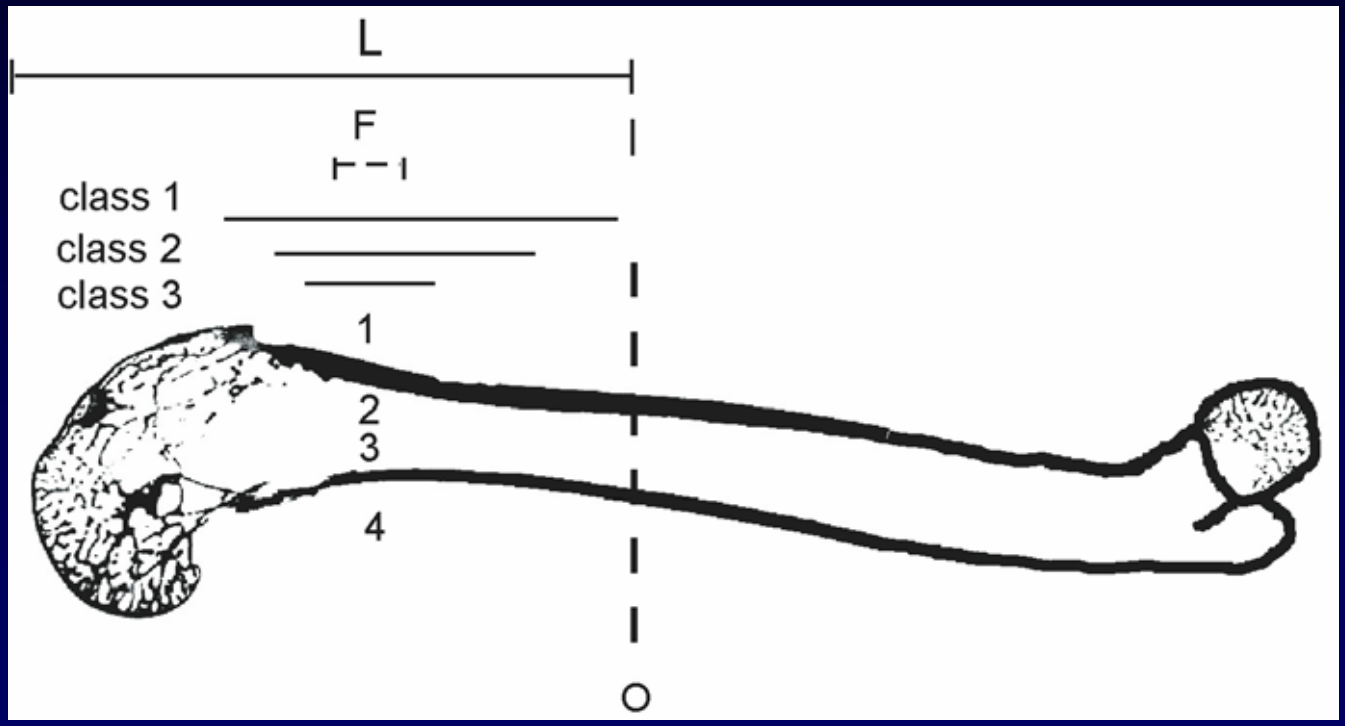
Do these results might tell us more about the mechanisms of action of shock waves on the musculo-skeletal system?

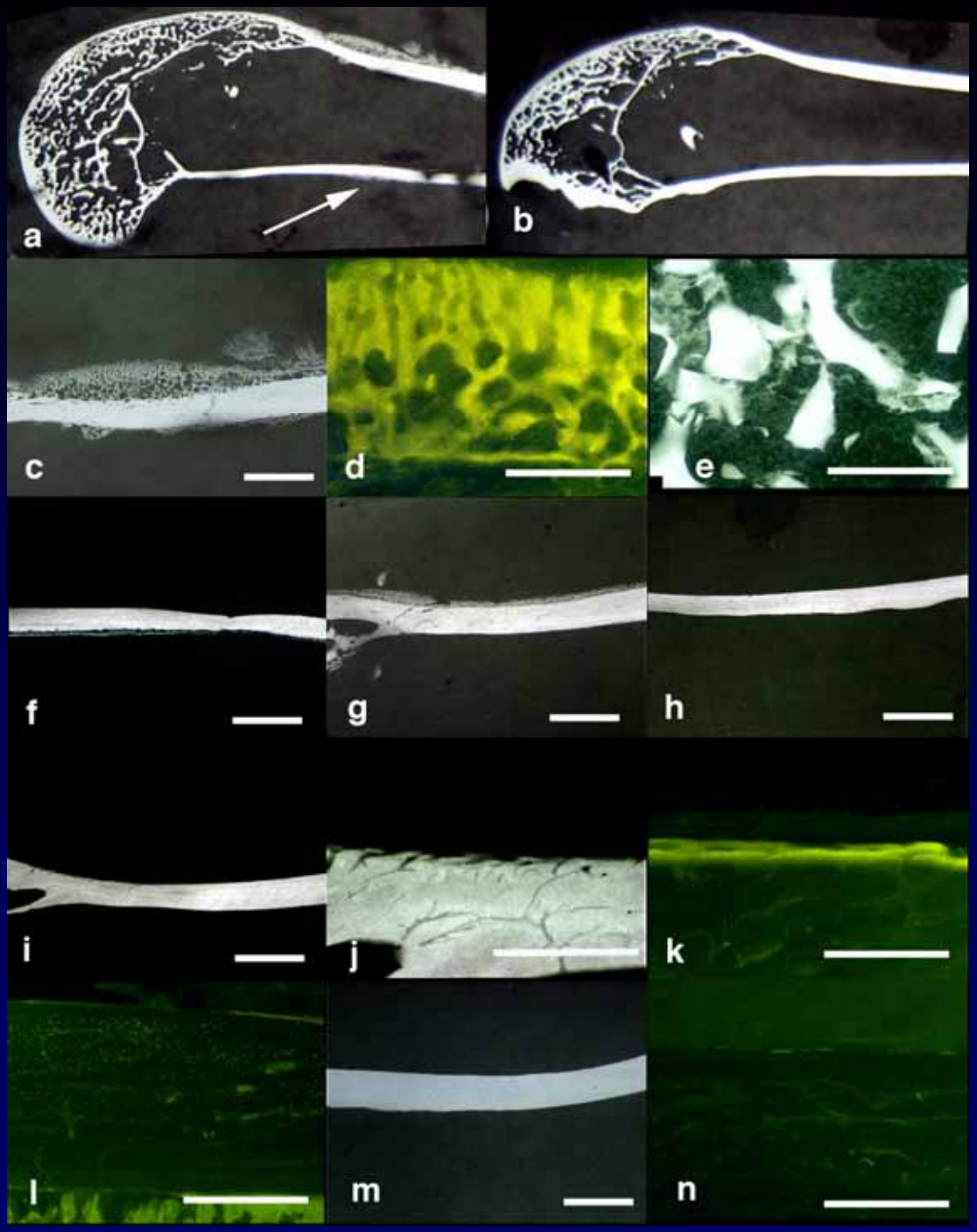
- Substance P is known to have osteogenic potential (Shih and Bernhard [1997], Adamus and Dabrowski [2001], Chole and Tinling [1998])

Study design (4)

- Rabbits (n=30)
- Application of extracorporeal shock waves *in vivo* to either the left or the right distal femur with 1,500 pulses at 1 / second and the following energy flux densities:
  - 0.0 mJ/mm^2 (n=6),
  - 0.35 mJ/mm^2 (n=6),
  - 0.5 mJ/mm^2 (n=6),
  - 0.9 mJ/mm^2 (n=6),
  - 1.2 mJ/mm^2 (n=6),
- S.c. injection of 25 mg/kg BW oxytetracycline (5) at varying sites of the back at the days 5 to 9 after shock wave application
- Analysis of bone structure and new bone formation 10 days after shock wave application

Study design (4)

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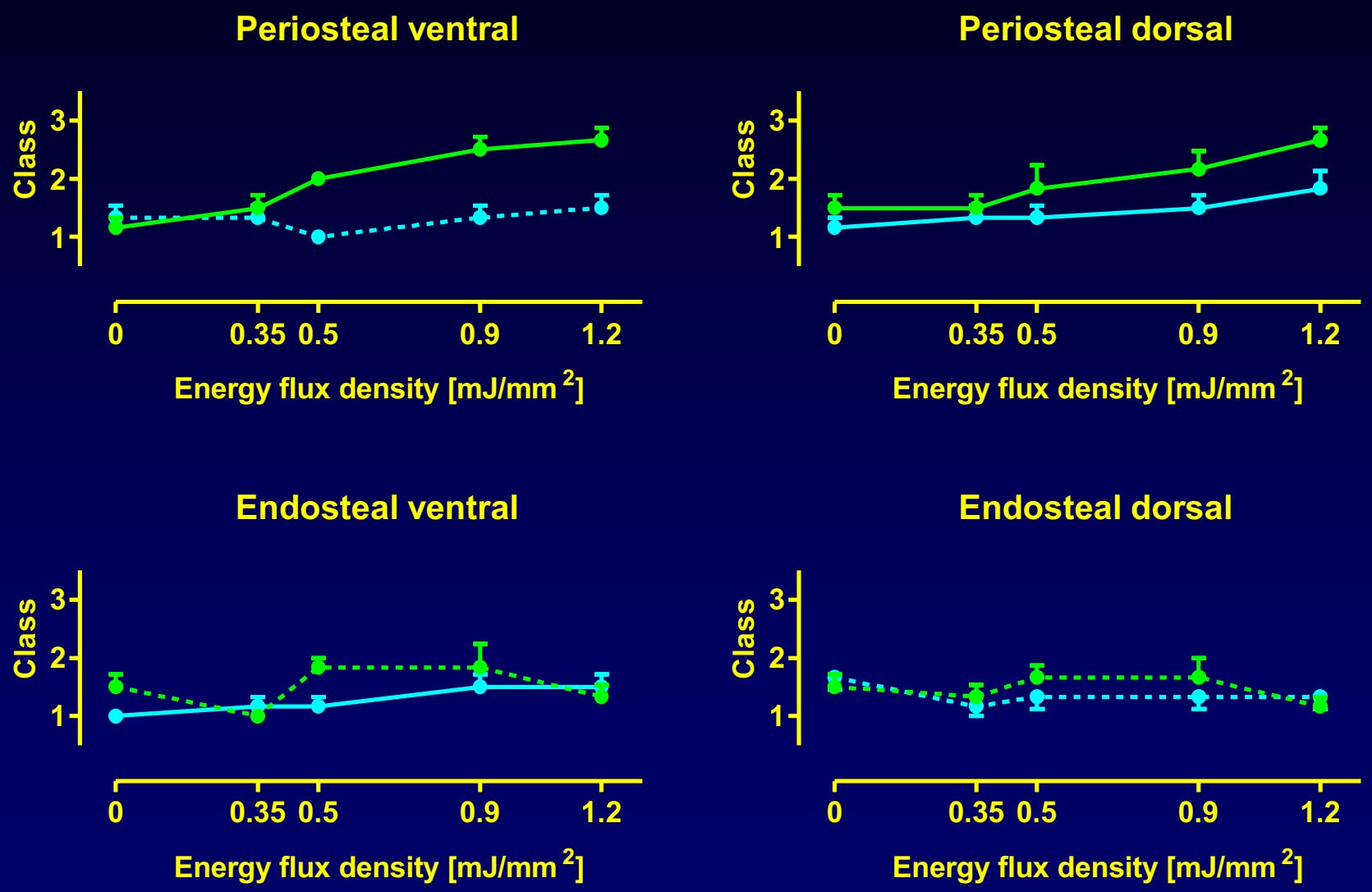
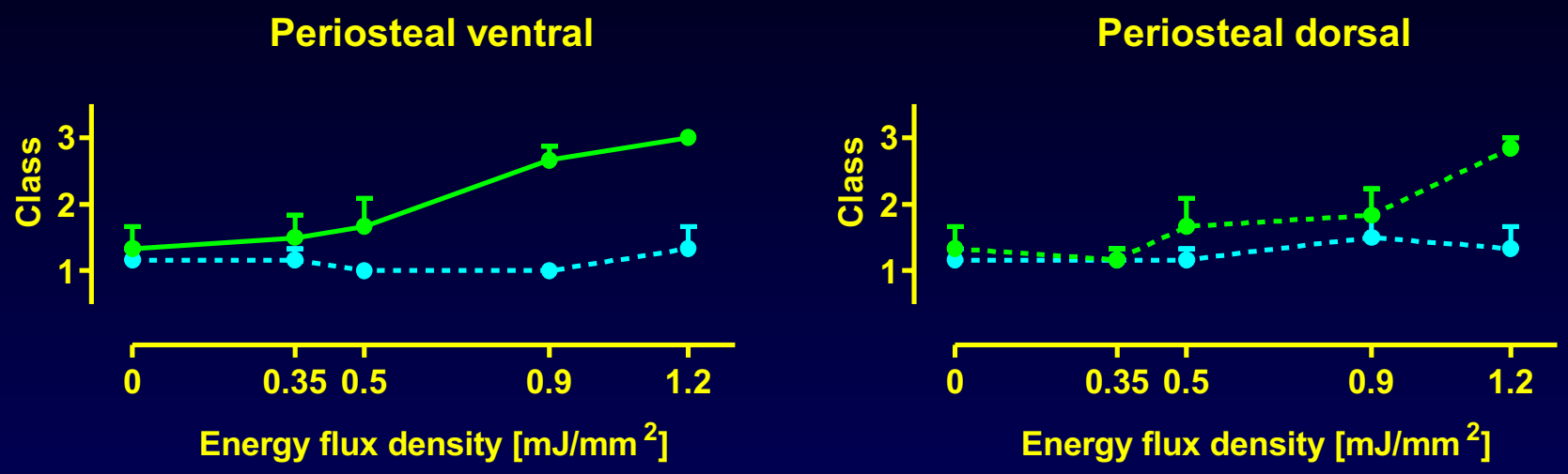
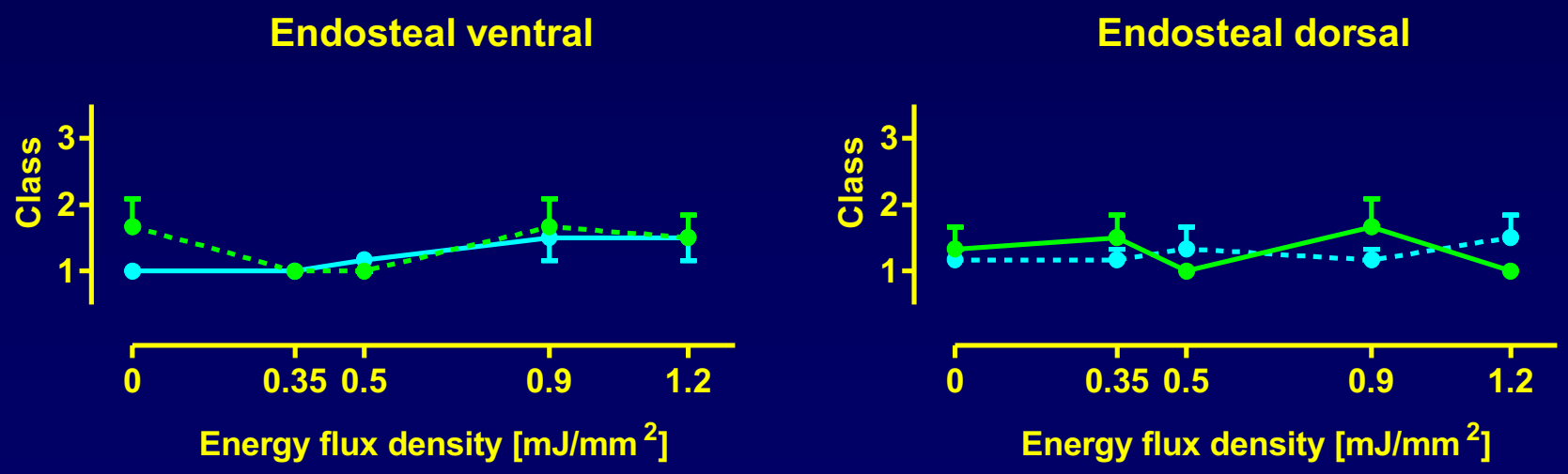
Formation of new bone - reaction type

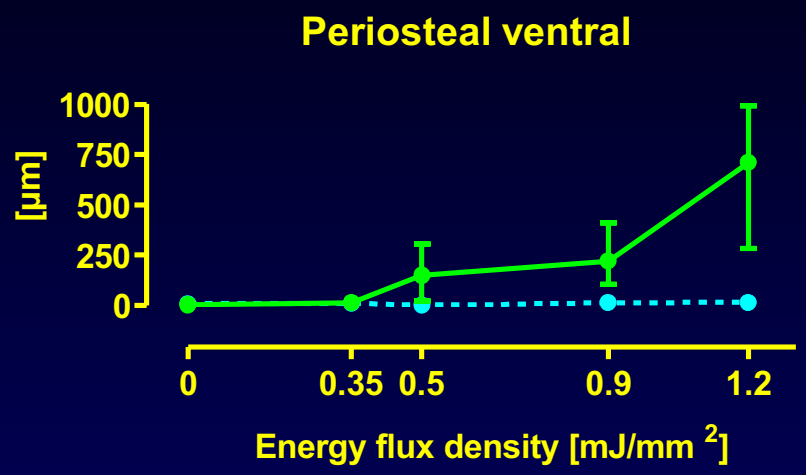


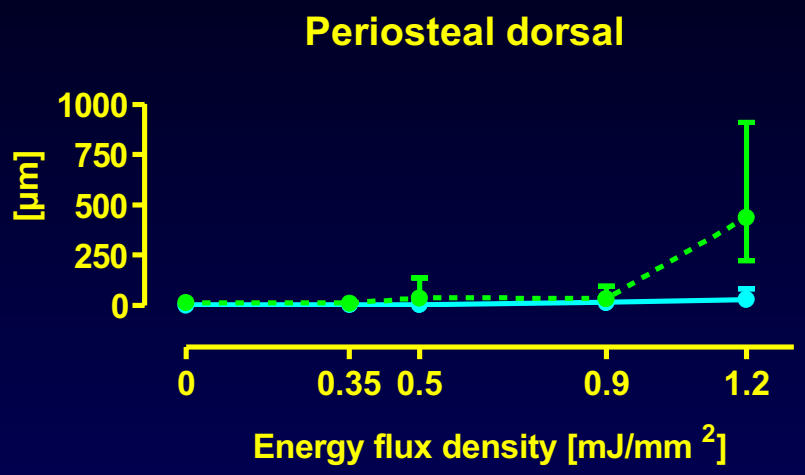
Formation of new bone - percentage

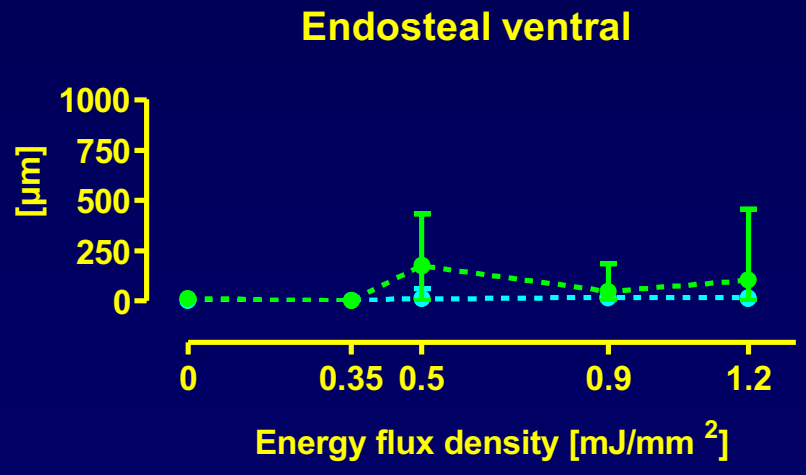


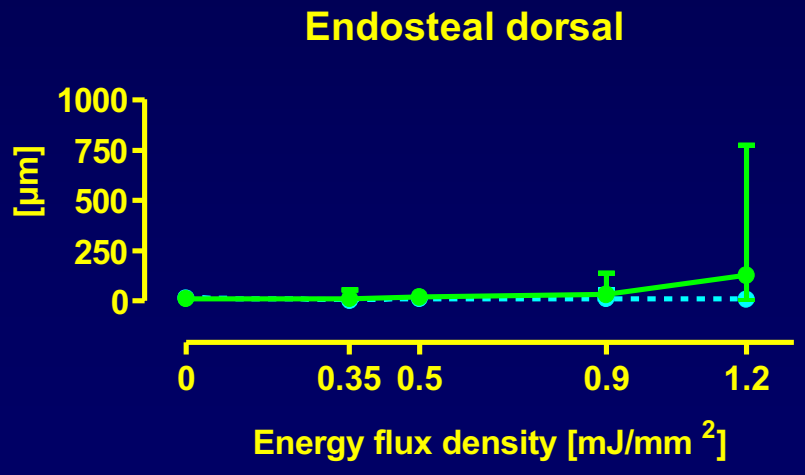


Form. of new bone - max. thickness

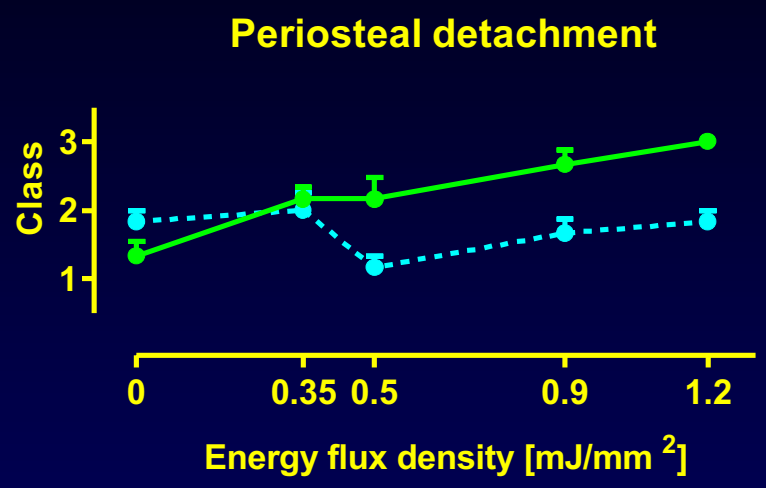


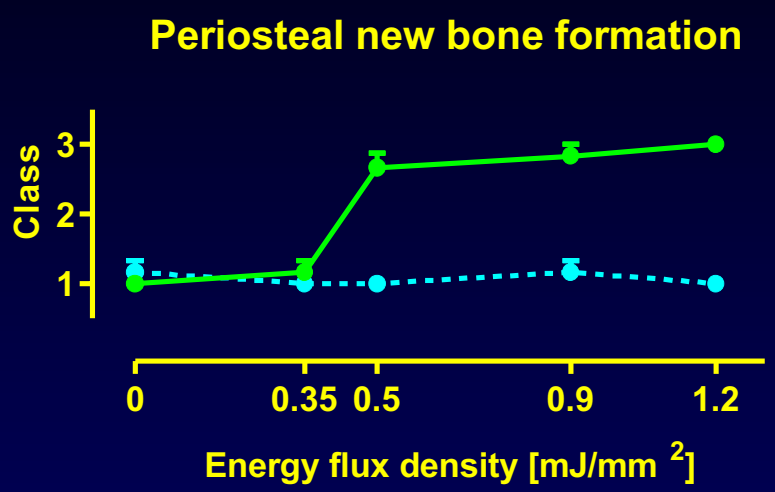


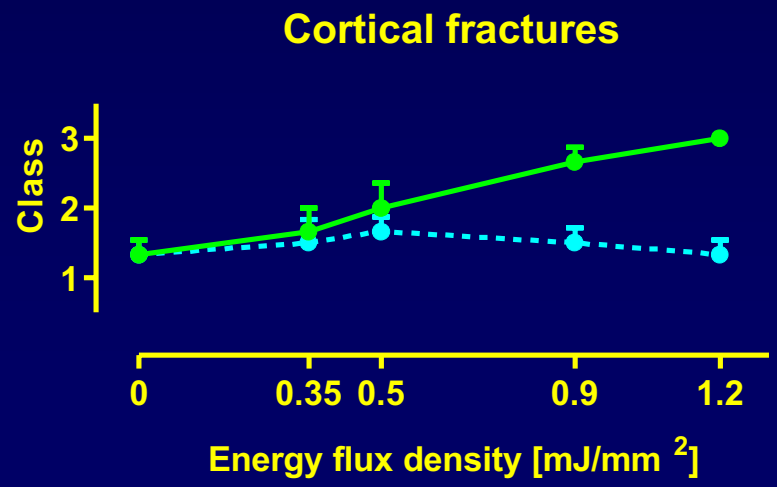


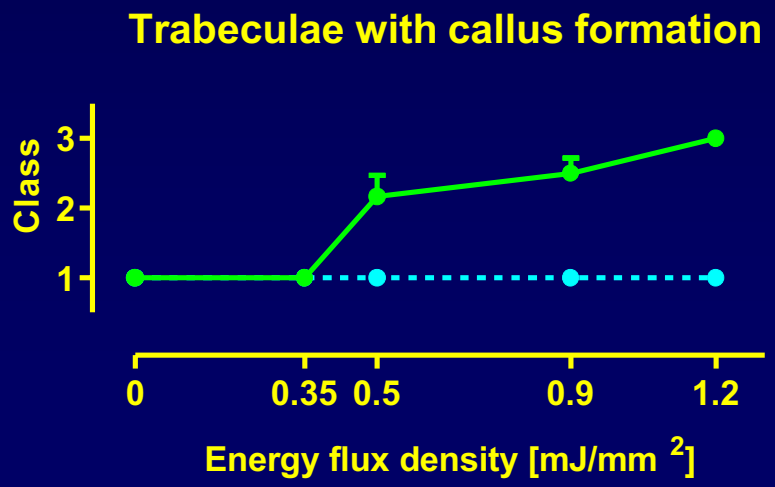


Bone - microradiography









Other results in the literature (1)

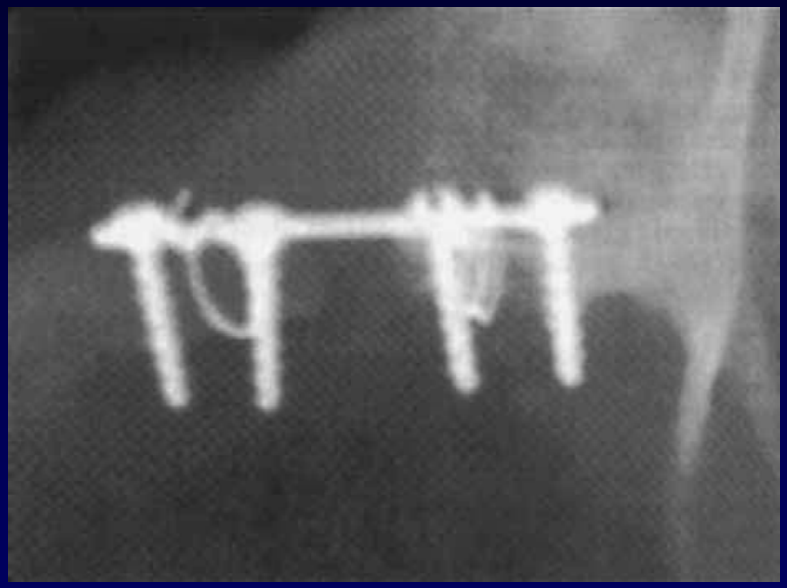
Temporal and spatial expression of bone morphogenetic proteins in extracorporeal shock wave-promoted healing of segmental defect.

Wang et al., Bone 2003;32:387-396

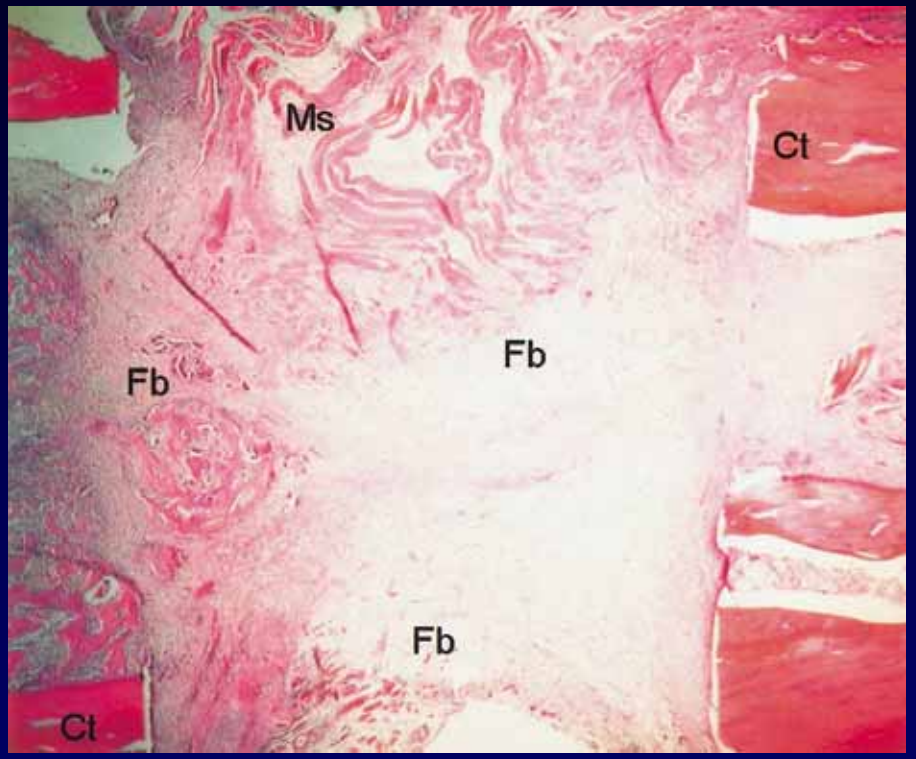
Study design (5)

- Rats (n=80)
- Midshaft femoral fracture (5 mm defect), stabilized with a miniplate (n=80)
- Application of extracorporeal shock waves *in vivo* to the femoral fracture with 500 pulses and an energy flux density of 0.16 mJ/mm^2 (n=40).
- Analysis of the rats after
  - 1 week (n=10 + 10)
  - 2 weeks (n=10 + 10)
  - 4 weeks (n=10 + 10)
  - 8 weeks (n=10 + 10)
- Analysis with rtPCR and immunohistochemistry

Results (5)

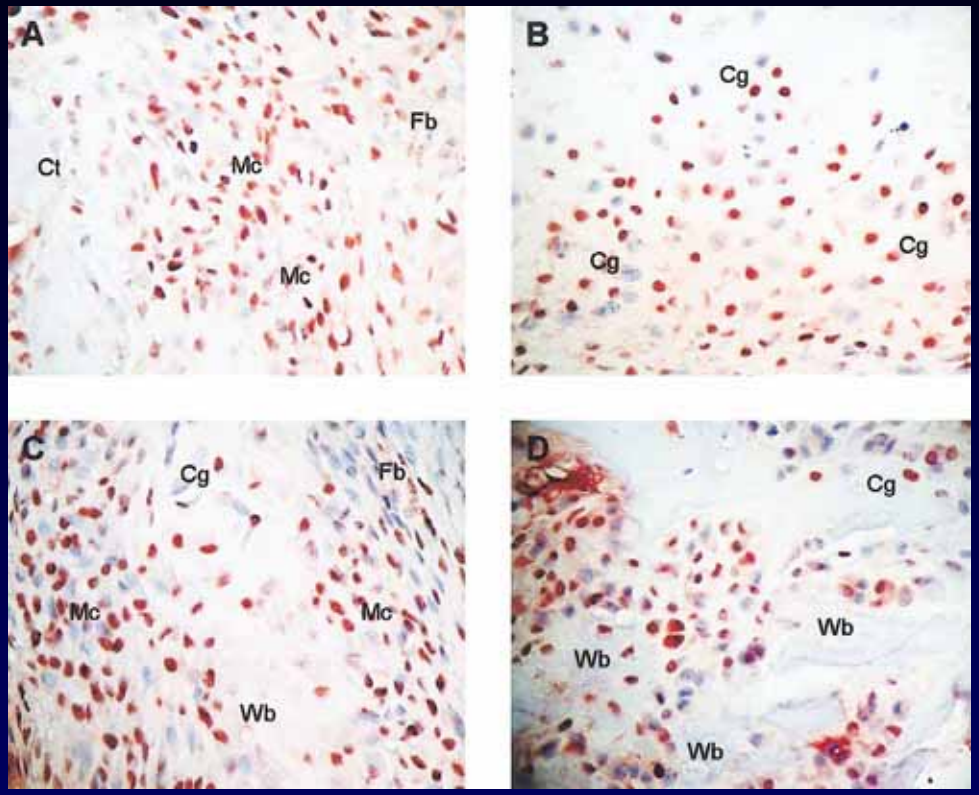


Segmented femoral defect, fixed with a miniplate.



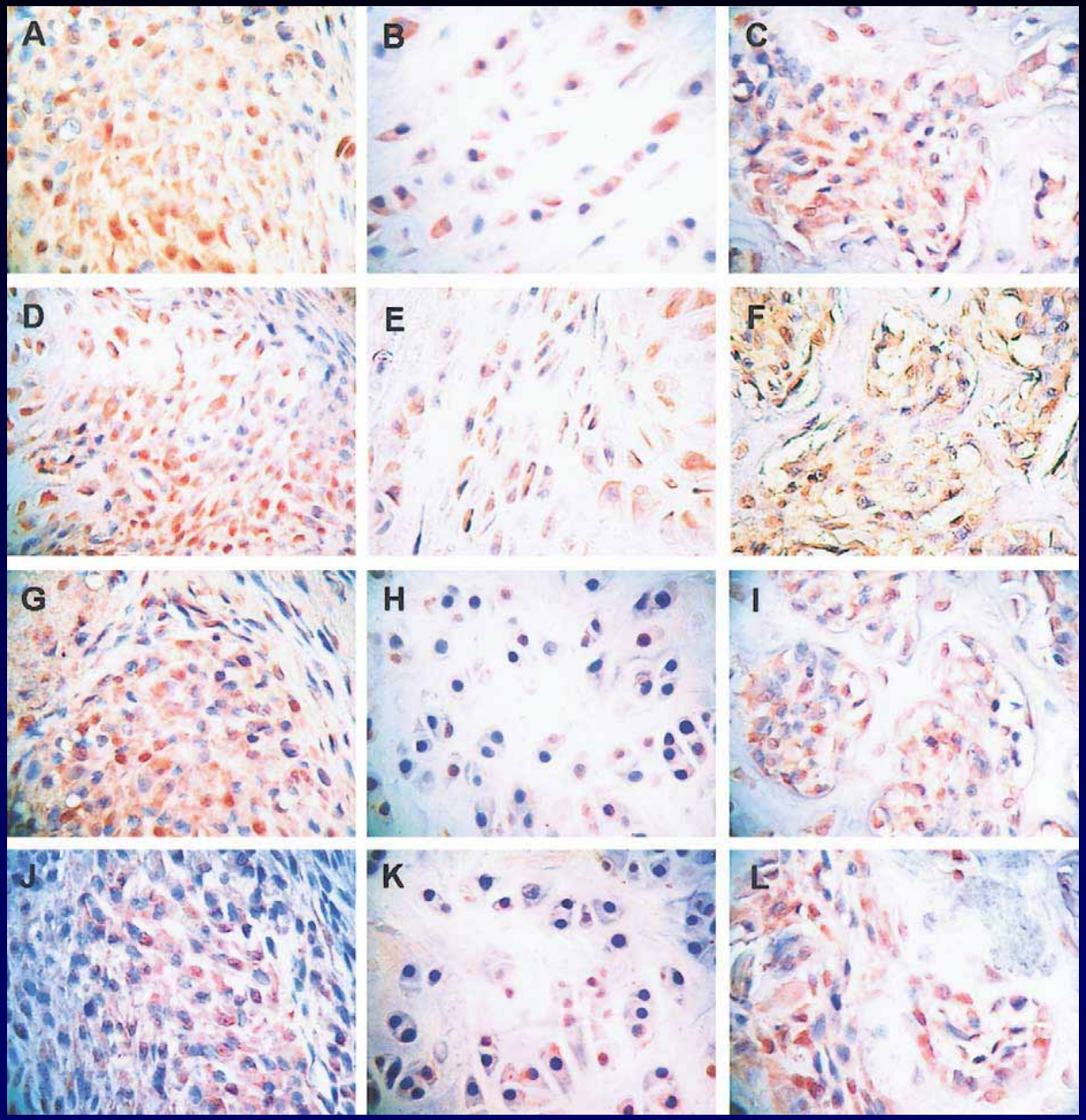
Segmented femoral defect. Fb, fibrous tissue; Ms, muscular tissue.

Results (5)



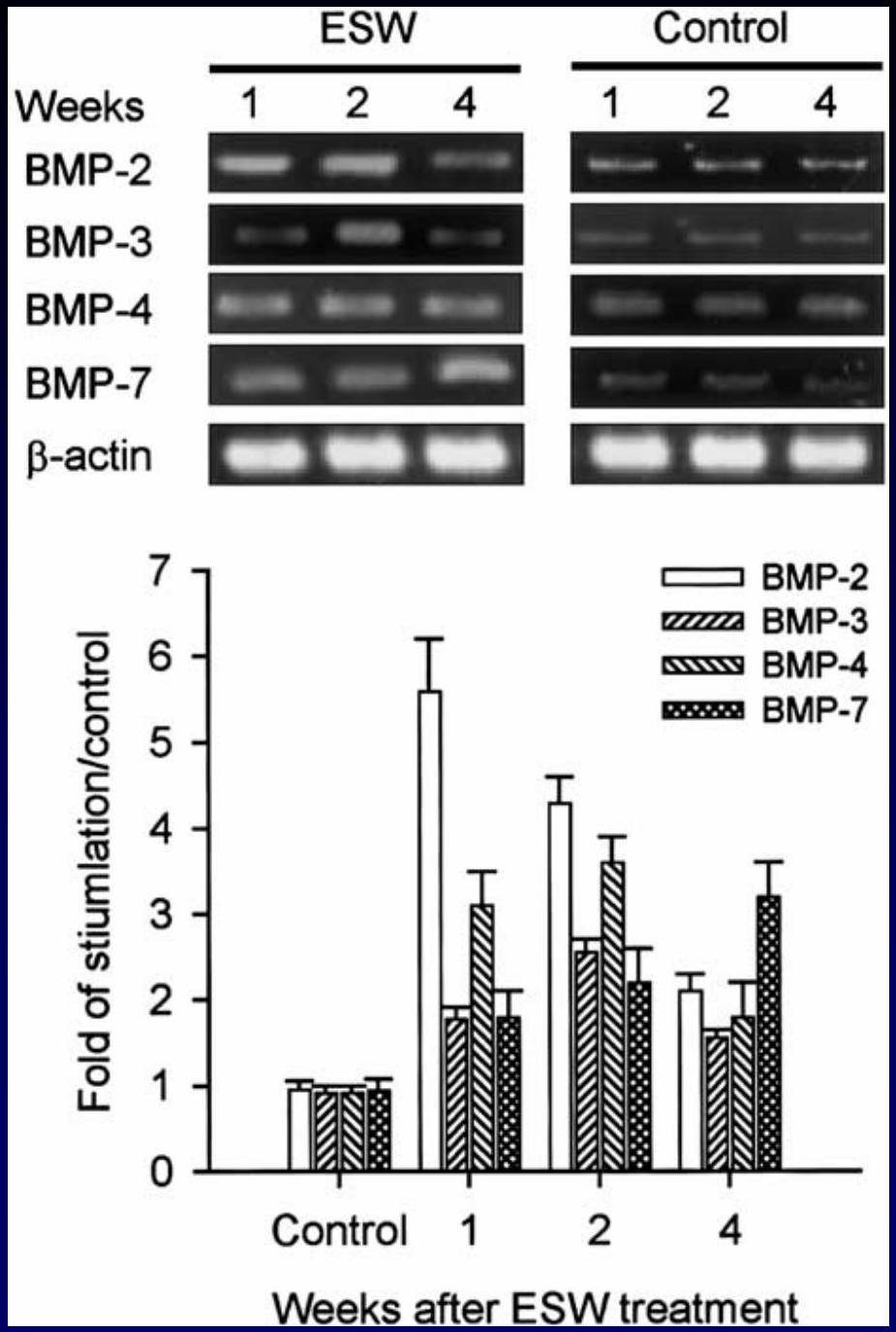
PCNA expression in ESW promotion of bone regeneration. (**A**) Aggregated mesenchymal cells show intensive PCNA staining. (**B** and **C**) Osteoblastic and chondral cells at the junction of the hypertrophic cartilage exhibits significant PCNA staining. (**D**) Osteoblasts adjacent to newly formed bone reveal marked PCNA expression. The positive PCNA-stained cells showed brown immunostaining in the nuclei. Fb, fibrous tissue; Cg, cartilage; Wb, woven bone.

Results (5)



Immunohistochemical photographs of ESW-promoted fracture healing. (**A**–**C**) BMP-2, (D–F) BMP-3, (G–I) BMP-4, (J–L) BMP-7. BMP expression in mesenchymal cells is shown in A, D, G, and J; BMP expression in chondrocytes is exhibited in B, E, H, and K; BMP expression in osteoblasts is shown in C, F, I, and L. The positive BMP-stained cells showed brown immunostaining.

Results (5)


ESW
Control
Weeks
1
2
4
1
2
4
BMP-2
BMP-3
BMP-4
BMP-7
β-actin
Fold of stiumlation/control
0
1
2
3
4
5
6
7
BMP-2
BMP-3
BMP-4
BMP-7
Control
1
2
4
Weeks after ESW treatment