ICPFDS for Tony Sheu's 60th Birthday

A Mathematical Model for the Instigation and Transmission of Biological and Neural Signals in Response to Acupuncture

Fudan Univerisity

Yao Wei

Happy Birthday, Tony

Wish you a happy and long life !

Content

- Background
- Experiment Foundation
- Model
- Method
- Results
- Conclusion and Discussion

NIH News Release -NIH ...

NIH NEWS RELEASE

NATIONAL INSTITUTES OF HEALTH — Office of the Director

FOR IMMEDIATE RELEASE
Wednesday, Nov. 5, 1997

Bill Hall
NIH Office of Medical Applications of Research
301-496-4819

Anita Greene
NIH Office of Alternative Medicine
301-496-7790

NIH Panel Issues Consensus Statement on Acupuncture

There are a number of pain-related conditions for which acupuncture may be effective as an adjunct therapy, an acceptable alternative, or as part of a comprehensive treatment program.

http://www.nih.gov/news/pr/nov97/od-05.htm

Background: the analgesic effect of acupuncture is well accepted

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作者: MAYER, DJ; PRICE, DD; RAFII, A
来源出版物: BRAIN RESEARCH 卷: 121 期: 2 页: 368-372 DOI: 10.1016/0006-8993(77)90161-5 出版年: 1977
被引频次: 438 (来自 Web of Science)
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2. 标题: Acupuncture
作者: Ramsay, DJ; Bowman, MA; Greenman, PE; 等.
团体作者: NIN Consensus Dev Panel Acupuncture
来源出版物: JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 卷: 280 期: 17 页: 1518-1524 出版年: NOV 4 1998
被引频次: 402 (来自 Web of Science)
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3. 标题: NALOXONE BLOCKADE OF ACUPUNCTURE ANALGESIA - ENDORPHIN IMPLICATED
作者: POMERANZ, B; CHIU, D
来源出版物: LIFE SCIENCES 卷: 19 期: 11 页: 1757-1762 DOI: 10.1016/0024-3205(76)90084-9 出版年: 1976
被引频次: 357 (来自 Web of Science)
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4. 标题: NEUROCHEMICAL BASIS OF ACUPUNCTURE ANALGESIA
作者: HAN, JS; TERENIUS, L
来源出版物: ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY 卷: 22 页: 193-220 DOI: 10.1146/annurev.pa.22.040182.001205 出版年: 1982
被引频次: 311 (来自 Web of Science)
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5. 标题: Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies
作者: Han, JS
来源出版物: TRENDS IN NEUROSCIENCES 卷: 26 期: 1 页: 17-22 文献号: PII S0166-2236(02)00006-1 DOI: 10.1016/S0166-2236(02)00006-1 出版年: JAN 2003
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6. 标题: Electroacupuncture: Mechanisms and clinical application
作者: Ulett, GA; Han, SP; Han, JS
来源出版物: BIOLOGICAL PSYCHIATRY 卷: 44 期: 2 页: 129-138 DOI: 10.1016/S0006-3223(97)00394-6 出版年: JUL 15 1998
被引频次: 265 (来自 Web of Science)
SFX 全文 [查看摘要]

7. 标题: Acupuncture: Theory, efficacy, and practice
作者: Kaptchuk, TJ
来源出版物: ANNALS OF INTERNAL MEDICINE 卷: 136 期: 5 页: 374-383 出版年: MAR 5 2002
被引频次: 242 (来自 Web of Science)
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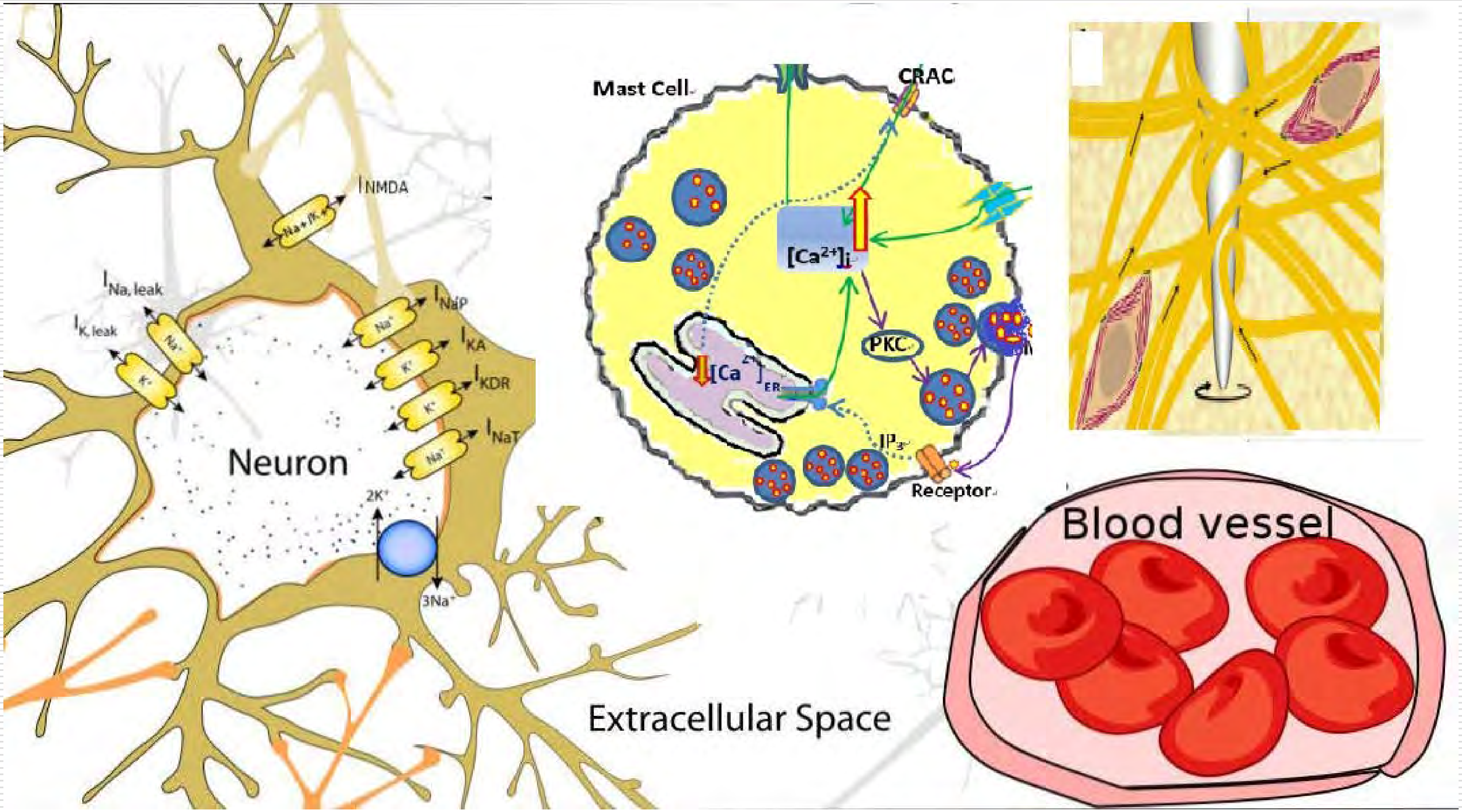
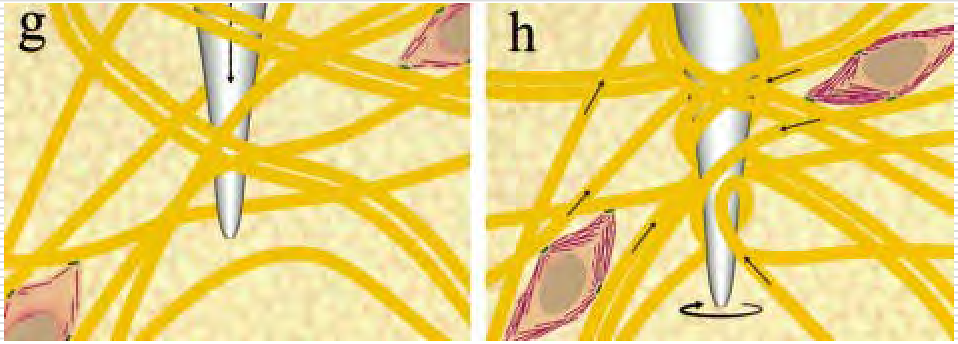
Background: the structural basis of the acupoints

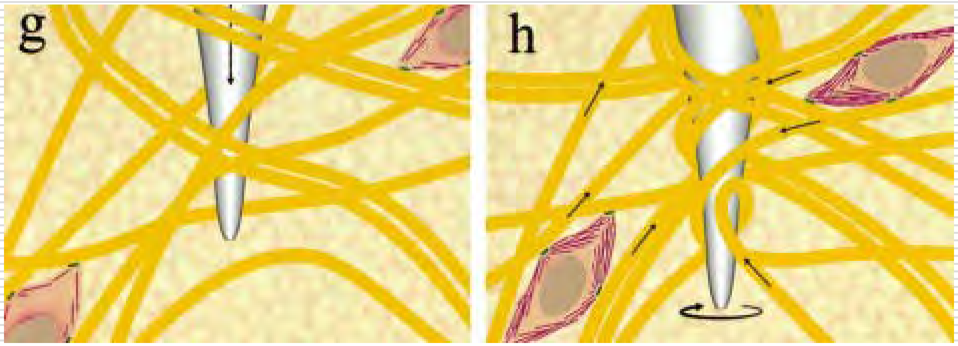


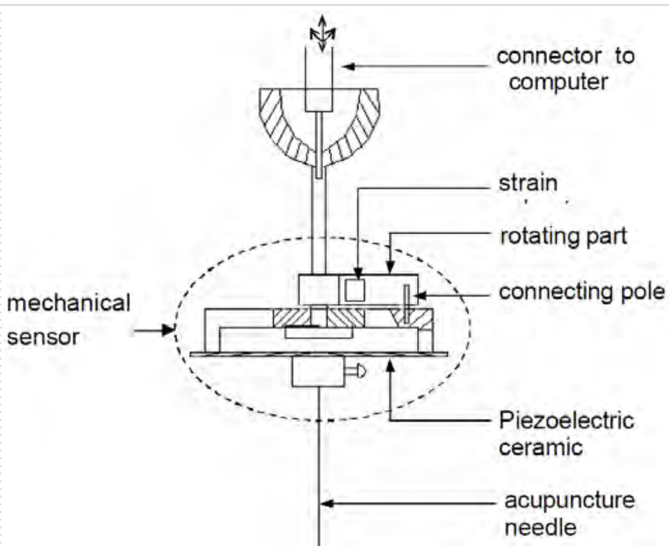
Background: Acupuncture, through winding tissue around the needle, transmits a mechanical signal to connective tissue cells via mechanotransduction



1. Langevin, H.M., Churchill, D.L. and Cipolla, M.J. Mechanical Signaling Through Connective Tissue: A Mechanism For The Therapeutic Effect Of Acupuncture.The FASEB Journal, 2001, 15: 2275-2282.
2. Langevin, H.M., Churchill, D.L., Fox, J.R., et al. Biomechanical response to acupuncture needling in humans. J Appl Physiol, 2001, 91(6):2471-2478.
3. Langevin, H.M.and Yandow, J.A. Relationship of acupuncture points and meridians to connective tissue planes. Anat Rec, 2002,269(6):257-265

Background： Acupuncture, through winding tissue around the needle, transmits a mechanical signal to connective tissue cells via mechanotransduction





I.J. Mechanical Signaling Through Connective Tissue: A Mechanism For
EB Journal, 2001, 15: 2275-2282.
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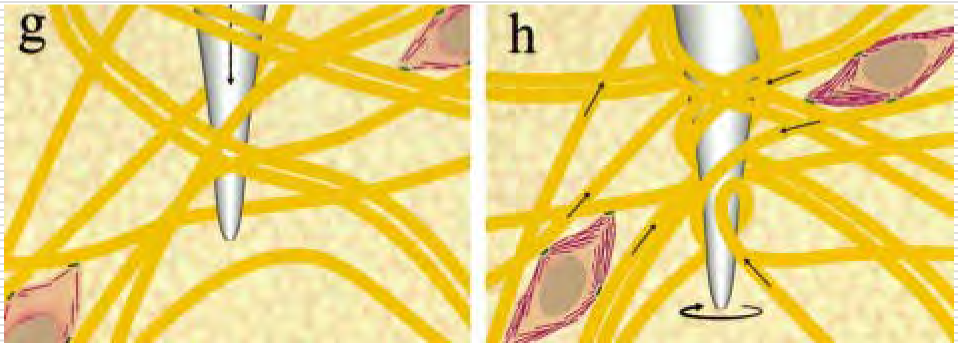
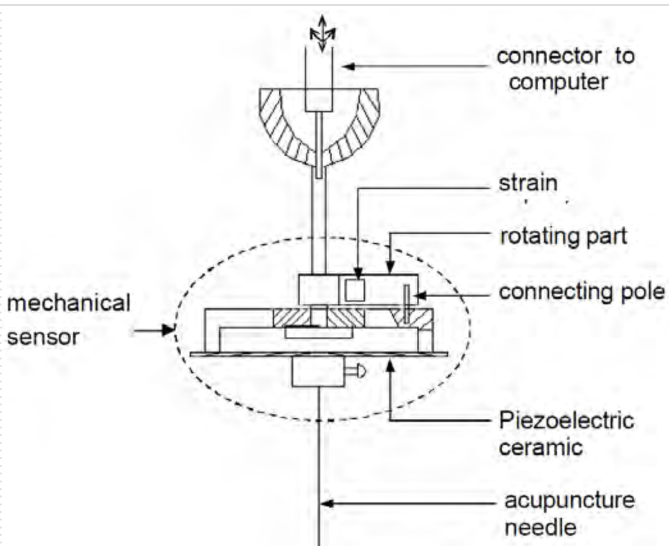
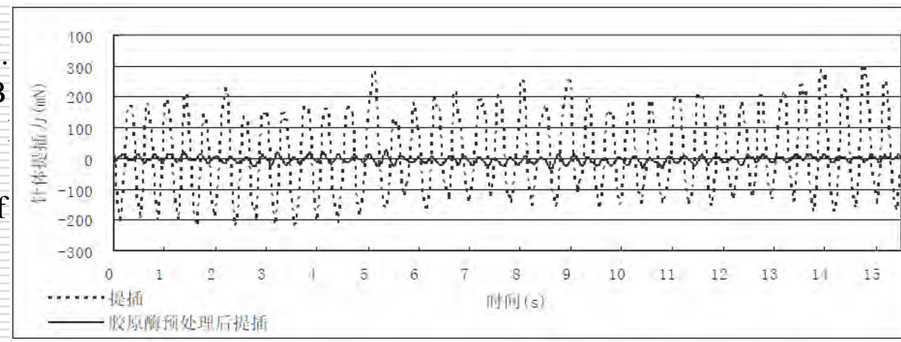
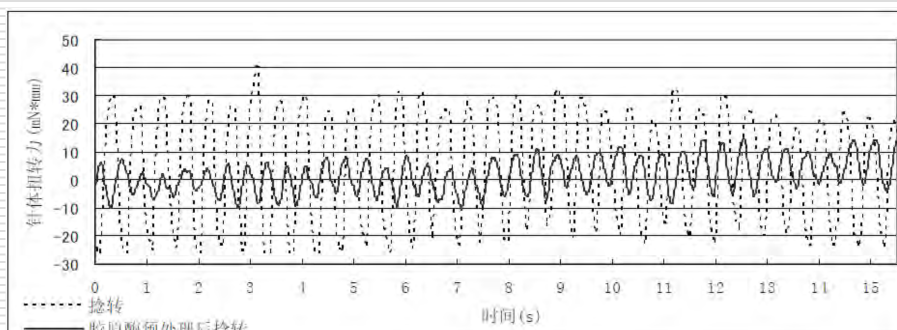
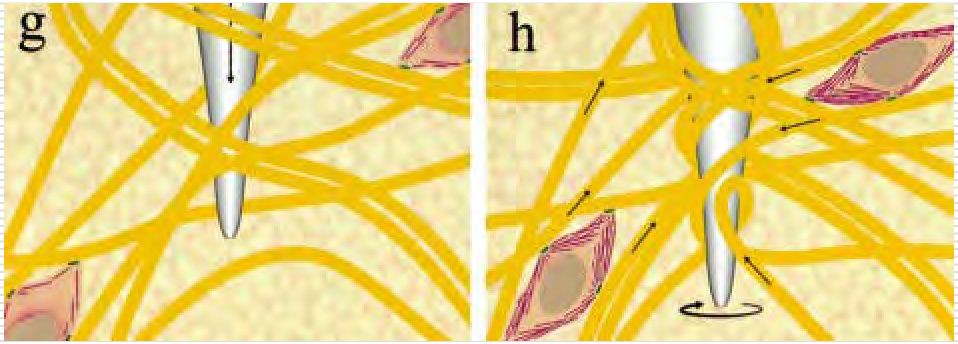


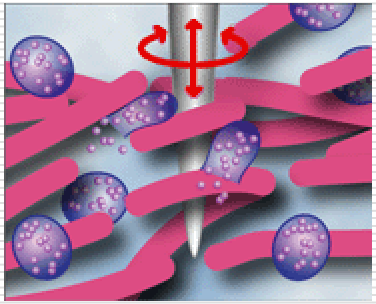






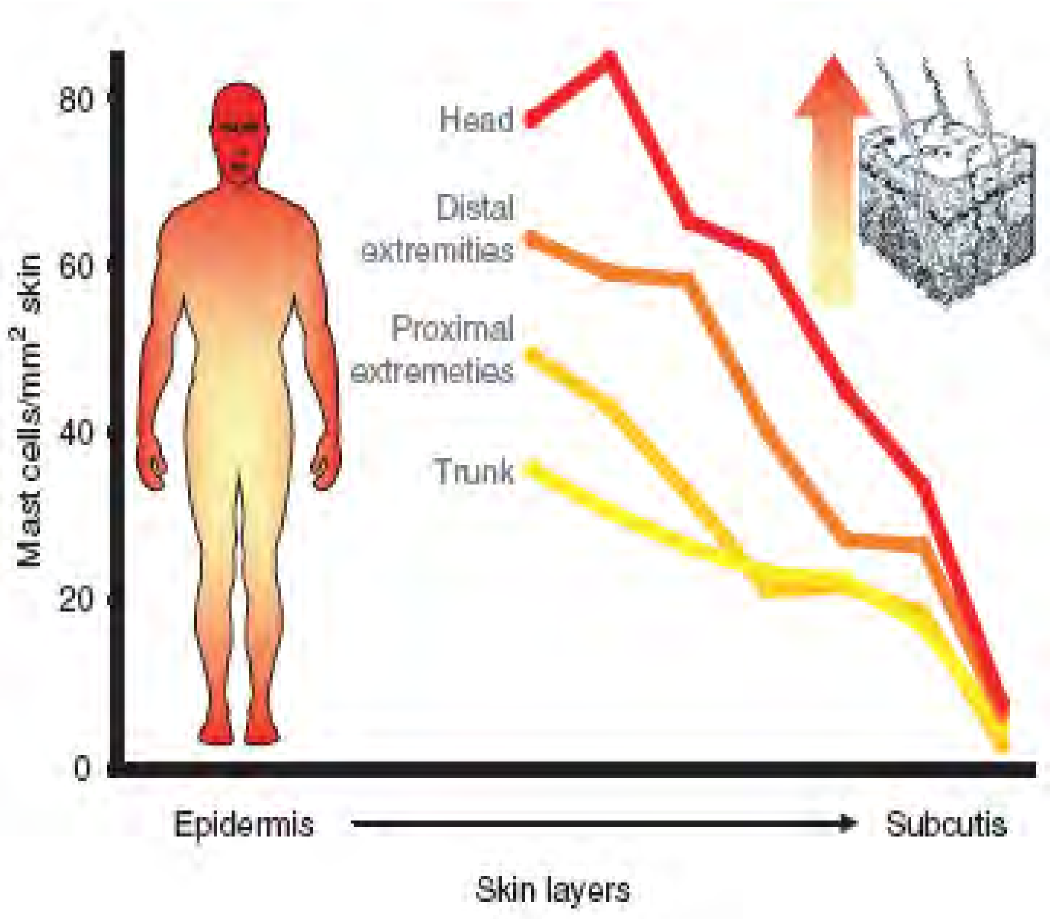
Background: **Acupuncture, through winding tissue around the needle, transmits a mechanical signal to connective tissue cells via mechanotransduction**





1. Langevin, H.M., Churchill, D.L. and Cipolla, M.J. Mechanical Signaling Through Connective Tissue: A Mechanism For The Therapeutic Effect Of Acupuncture.The FASEB Journal, 2001, 15: 2275-2282.
2. Langevin, H.M., Churchill, D.L., Fox, J.R., et al. Biomechanical response to acupuncture needling in humans. J Appl Physiol, 2001, 91(6):2471-2478.
3. Langevin, H.M.and Yandow, J.A. Relationship of acupuncture points and meridians to connective tissue planes. Anat Rec, 2002,269(6):257-265
4. Ding Guanghong, Yu XJ. **Yao Wei**. Function of gollagen fiber type I in acupoints during acupuncture analgesia at ZUSANLI on rats. Journal of alternative and complemetary medicine. 2007, 13(8): 893
5. Yu XJ. Ding Guanghong. Huang H. Lin J**. Yao Wei**. Zhan Y. Role of Collagen Fibers in Rat Zusanli Acupoint (ST36) during Acupuncture Analgesia Therapy, Connective Tissue Research, 2008, 50 (2): 110-120

Background： Mast cell are the first defection of body



MCs are an integral component of the immune system, which resident at the interface between the body and the external environment enabling them to respond rapidly to environmental stimuli, and making them 'sentinels' of the immune system

Weber A. Knop J. Maurer M. Pattern analysis of human cutaneous mast cell populations by total body surface mapping. British Journal of Dermatology. 148: 224-228 (2003)

Background： Critical protective role of mast cells

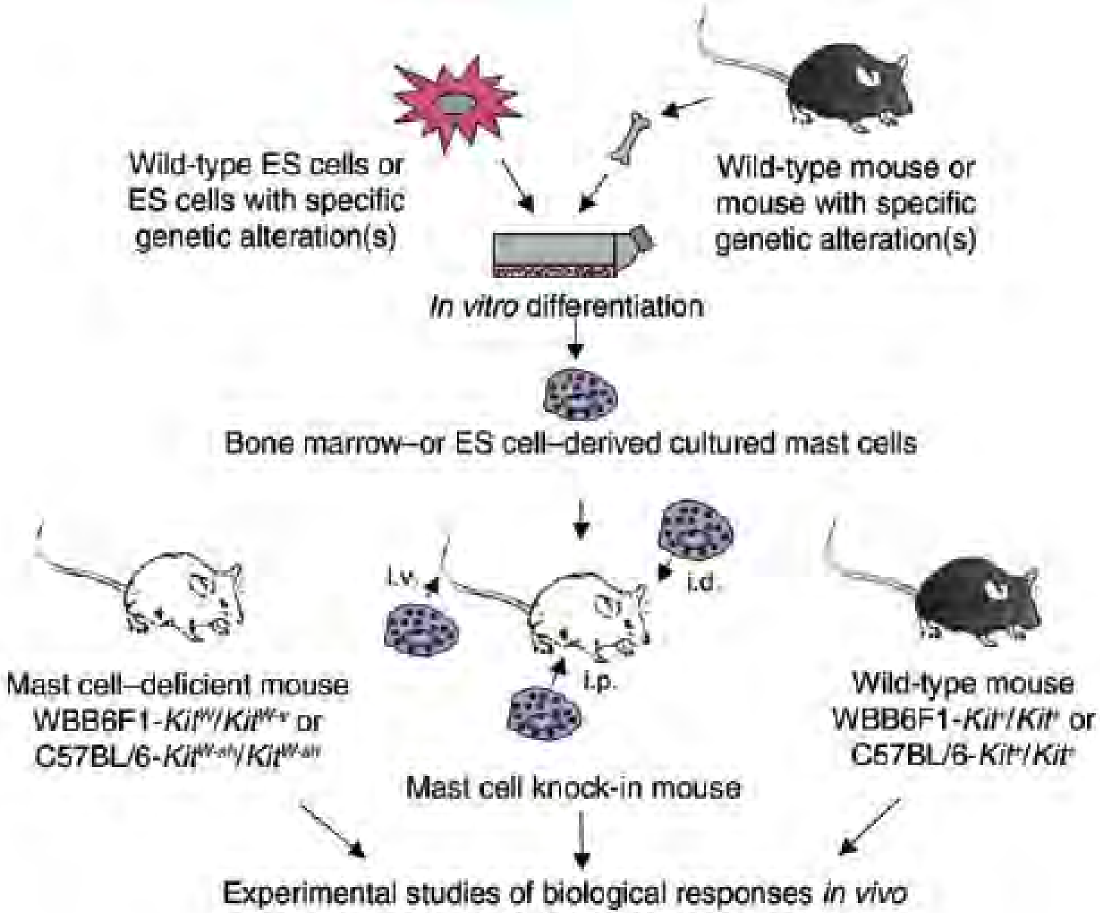
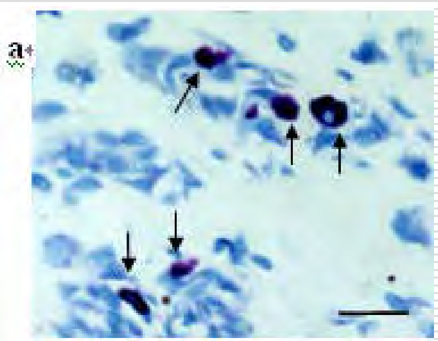


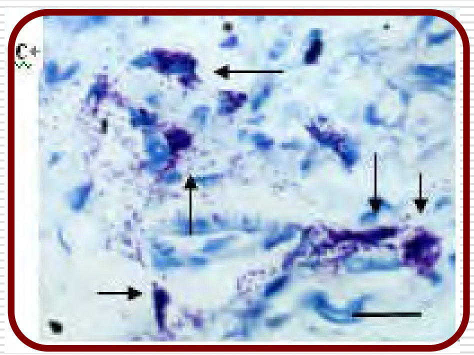
Figure 1 Mast cell knock-in mouse model for *in vivo* analyses of mast cell function. Mast cells are generated from bone marrow cells (or other hematopoietic cells; for example, those in the fetal liver) from wild-type mice or from mice with specific genetic alterations. Alternatively, embryonic stem cell–derived cultured mast cells can be generated from wild-type or genetically-altered embryonic stem cells. These bone marrow– or embryonic stem cell (ES)–derived cultured mast cells can then be transplanted intravenously (i.v.), intraperitoneally (i.p.) or intradermally (i.d.) into mast cell–deficient c-Kit mutant mice, such as WBB6F1-$Kit^{W}/Kit^{W\text{-}v}$ or C57BL/6-$Kit^{W\text{-}sh}/Kit^{W\text{-}sh}$ mice, to produce mast cell knock-in mice. Mast cell function(s) in biological responses can be analyzed by comparison of the responses in wild-type, mast cell–deficient and selectively mast cell–reconstituted mice. The contributions of specific mast cell products (surface structures, signaling molecules, secreted products and so on) are analyzed by comparison of the production of the responses of interest in mast cell knock-in mice reconstituted with wild-type mast cells versus mast cells derived from mice or embryonic stem cells that lack or express genetically altered forms of such products.

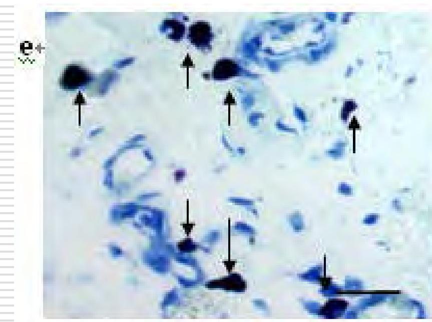
•Echtenacher B. Mannel DN. Hultner L. **Critical protective role** of mast cells in a model of acute septic peritonitis. Nature 1996: 381: 75-77

Background: **Mechanical stimuli of acupoint is associated with mast cell degranulation and that degranulation correlated with acupuncture effect**

1 张迪，丁光宏, 沈雪勇等. 肥大细胞功能对针刺大鼠“足三里”镇痛效应的影响, 针刺研究, 2007, 32(3):147-152
2 Zhang D, Ding Guanghong, Schwarz W. Cellular Mechanisms in Acupuncture-induced Mast Cell Degranulation. Journal of alternative and complemetary medicine. 2007, 13(9): 899,
3 Zhang D, Ding Guanghong, Sgen X, et al, Role of mast cells in acupuncture effect: a pilot study. Explore-the journal of science & healing, 2008, 4(3): 170-177
4 Yao, Wei. Li YB. Ding GH. Interstitial Fluid Flow: The Mechanical Environment of Cells and Foundation of Meridians. Evidence-Based Complementary and Alternative Medicine. Article ID 853516, 9 pages doi:10.1155/2012/853516
5 Yao, Wei. Ding G.H., Interstitial fluid flow: simulation of mechanical environment of cells in the interosseous membrane, Acta Mechanica Sinica. 27: 602–610 (2011)





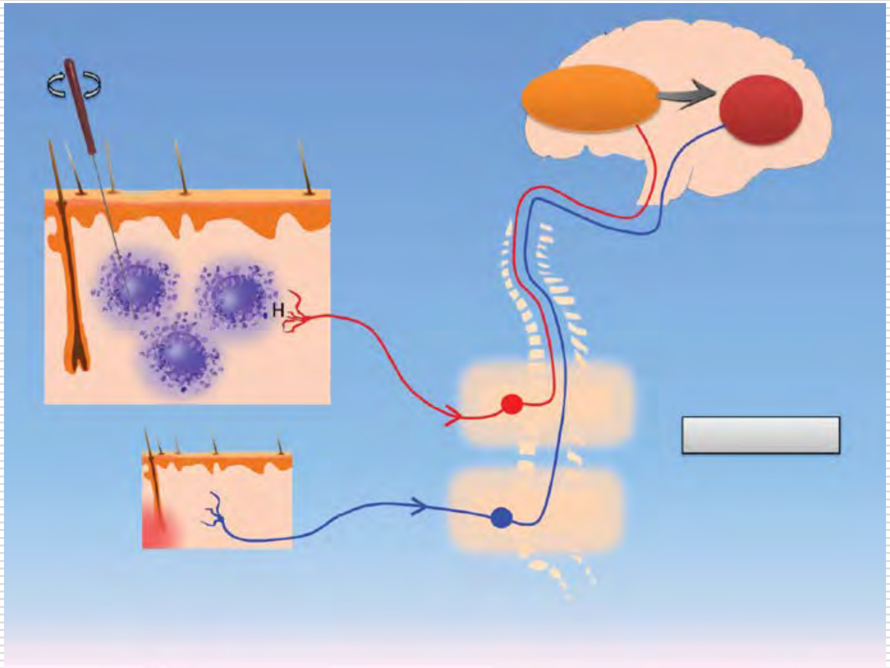


Mast cell at acupoint

Mast cell after acupuncture

Mast cell after acupuncture + DSCG

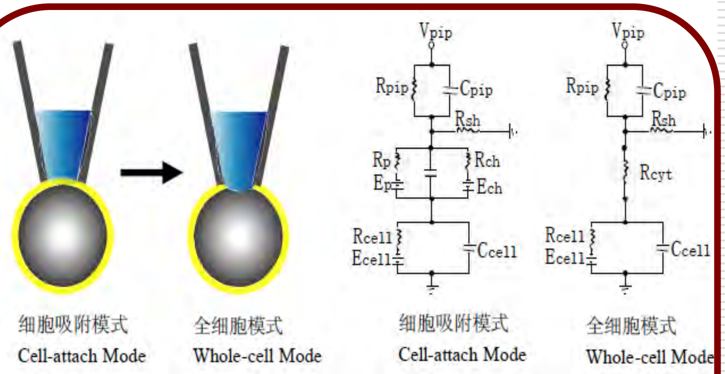
Background： acupuncture analgesia depend on the neural system, and there’s no acupuncture effect when the acupoint is narcotized



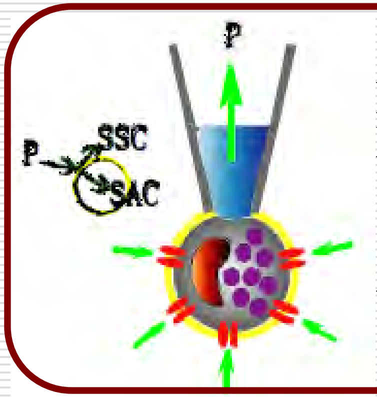
Mast cells are activated by the mechanical force through the manipulation of the needle. The biomediators release from mast cells activated the nerve cells. Since the acupoint is away from the pain site, it is not interrupted by the activation of the pain sensation but activates the target in the brain and initiates acupuncture analgesia.

N. Goldman, M. Chen, T. Fujita, et al. Adenosine A1 Receptors Mediate Local Anti-Nociceptive Effects of Acupuncture. Nat Neurosci, 13(7): 883-888, 2010
Huang M., Zhang D., Sa ZY. et al. In Adjuvatn-induced Arthritic Rats, Acupuncture Analgesic Effects are Histamine Dependent: Potential Reasons for Acupoint Preference in Clinical Practice. Evidence-based Complementary and Alternative Medicine. 2012. Article ID 810512, 6 pages. doi:10.1155/2012/810512

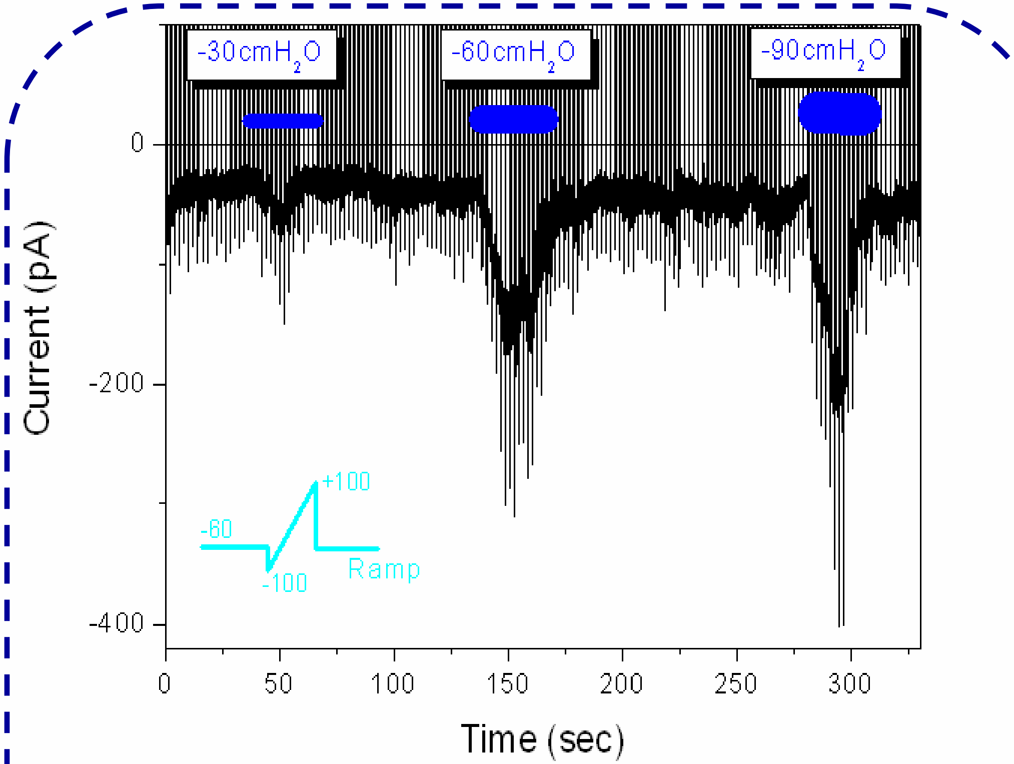
Experiment 1： Membrane current under mechanical stimuli



The schematic drawing (left) and equivalent circuit (right) of on-cell patch mode and whole-cell patch mode



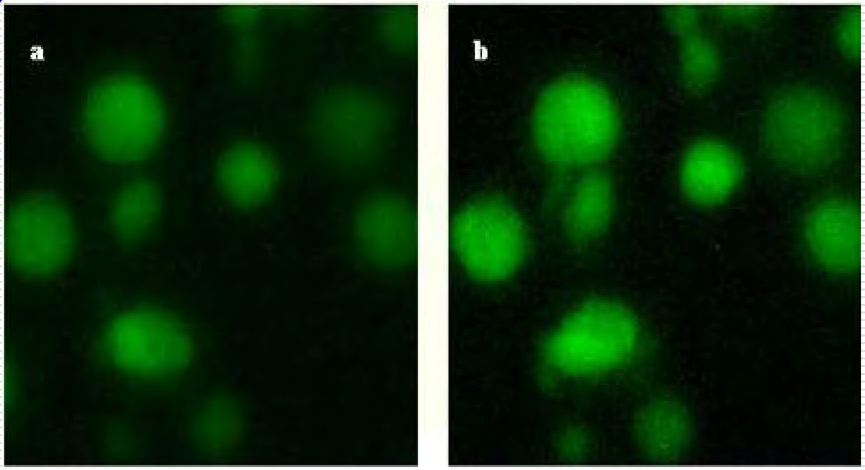
A cell is opposed to a mechanical force P that generates at the cell is opposed to a force perpendicular to the surface



Activation of membrane currents by membrane stretch of 30, 60 and 90 cm H2O negative pressure in the whole cell patch-clamp configuration。

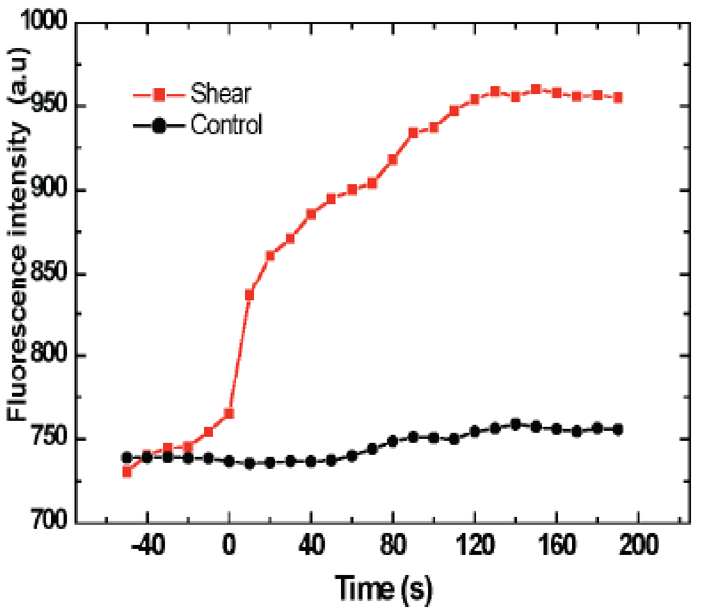
Zhang Di, Spielmann A, Ding Guanghong*, Activation of Mast-cell Degranulation by Different Physical Stimuli Involves Activation of the Transient-receptor-potential Channel TRPV2, Physiological research, 2012, 61(1): 113-124

Experiment 2: Ca^{2+} rise under mechanical stimuli



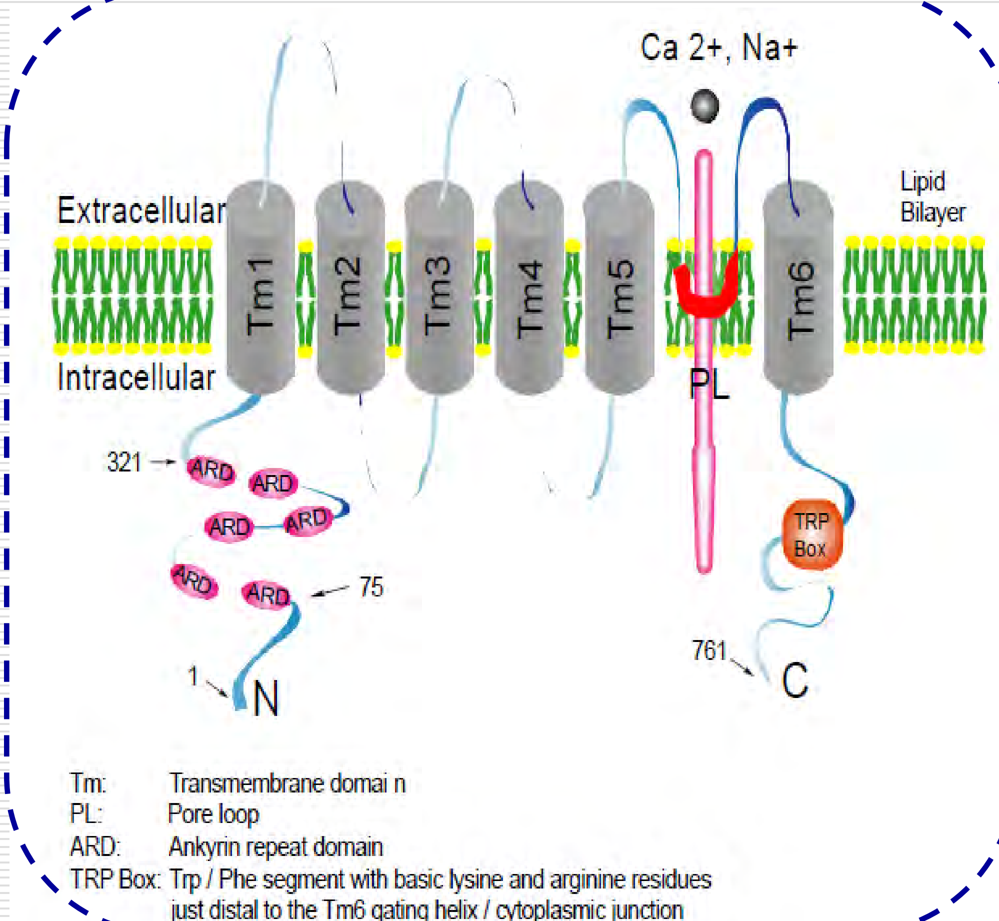
Ca^{2+} signal, (a) isotonic solution, (b) hypotonic solution

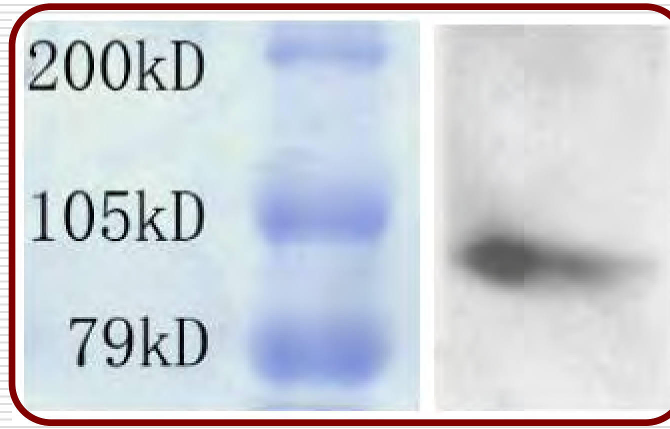
Ca^{2+} signal in MCs under shear stress



Wang, L.N.: Investigation of mechanical sensitive channels on mast cell. [PhD Thesis]. Shanghai: Fudan university, (2010) (in Chinese)
Yang, WZ. Chen JY. Zhou LW. Effects of Shear Stress on Intracellular Calcium Change and Histamine Release in Rat Basophilic Leukemia (RBL-2H3) Cells. Joural of Environmental pathology and oncology. 2009, 28(3):

Experiment 3： Presence of TRPVs protein in Mast cell



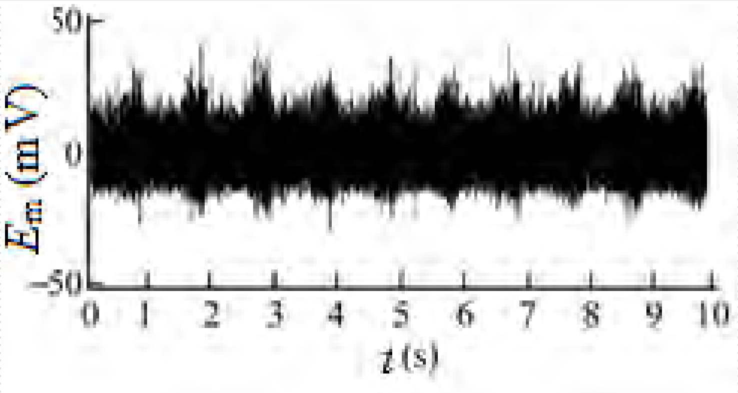


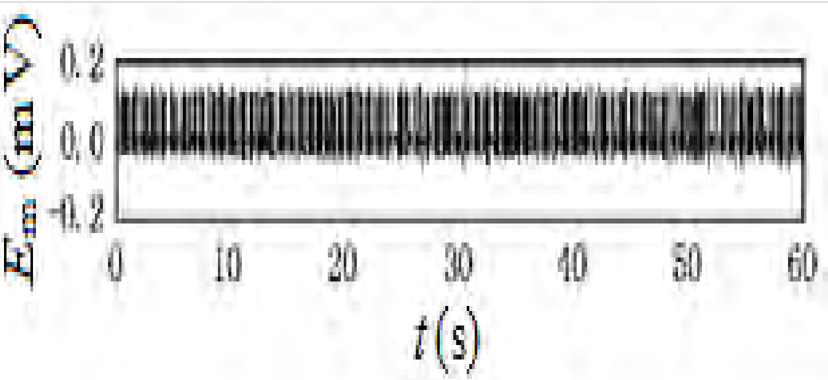
TRPV2 expression in HMC-1

TRPV4 expression in RBL-2H3

Zhang D. Involvement of the Function of Mast Cells in Acupuncture Analgesia and the Sensitivity of HMC-1 to Mechanical, Thermo and Light Stimulation in TCM Treatment. . [PhD Thesis]. Shanghai: Fudan university, (2008) (in Chinese)
Yang, WZ. Chen JY. Zhou LW. Effects of Shear Stress on Intracellular Calcium Change and Histamine Release in Rat Basophilic Leukemia (RBL-2H3) Cells. Joural of Environmental pathology and oncology. 2009, 28(3):

Experiment 4: Action potential recorded in neurons acupuncture at ST36

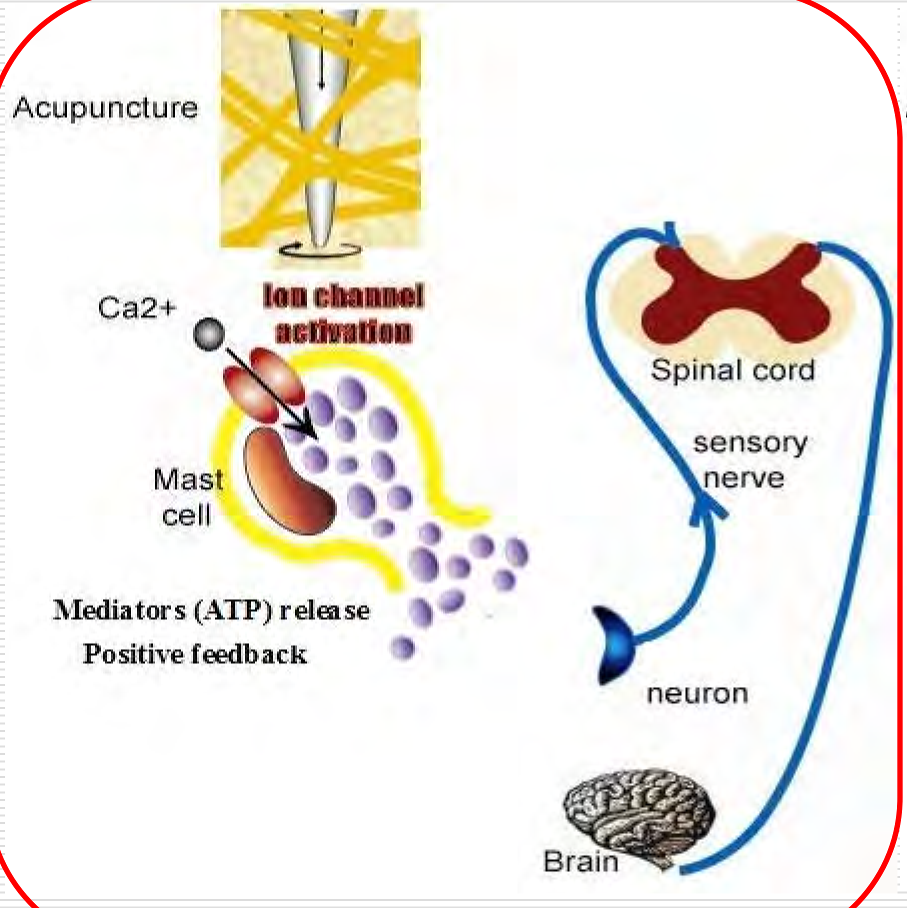




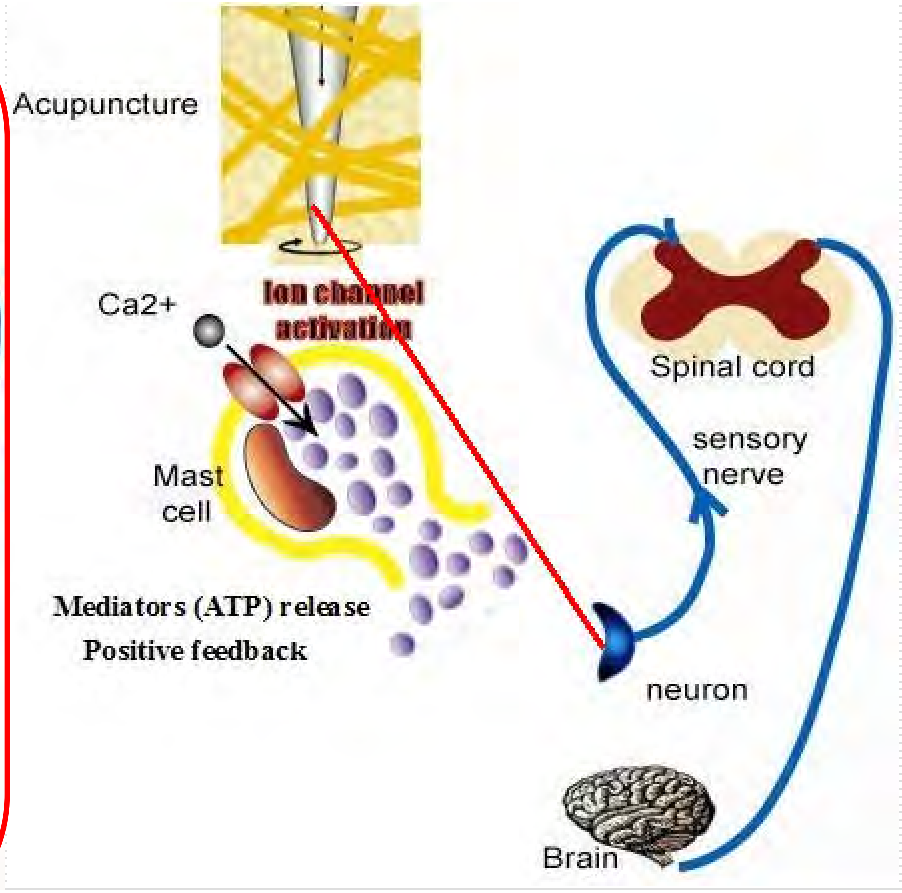
(a) (b)

Fig E_m induced by acupuncture. (a) E_m in the sensory neuron. (b) E_m in the spinal cord neuron.

Hypotensis

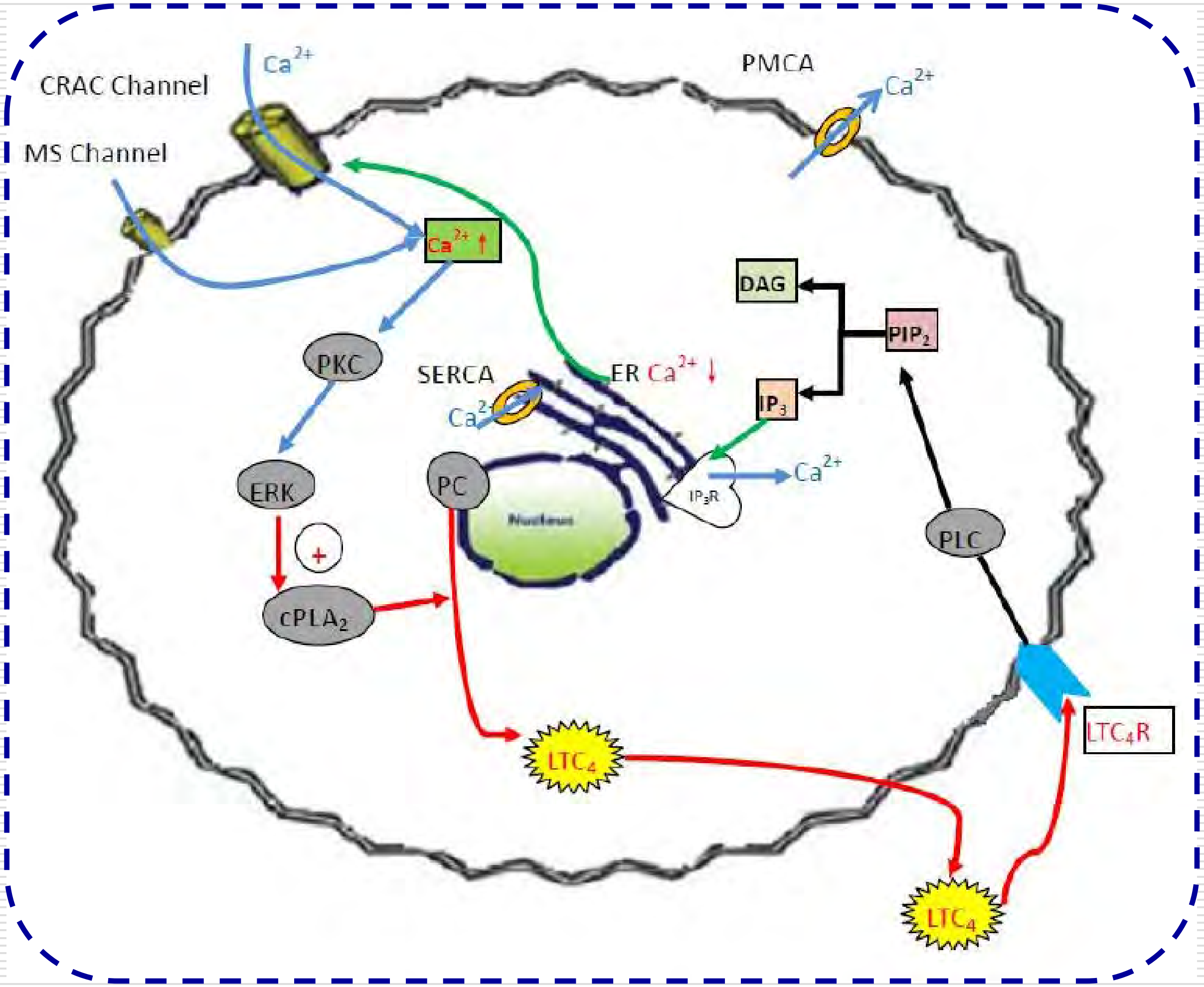


Acupuncture
Ca2+
Ion channel activation
Mast cell
Mediators (ATP) release
Positive feedback
Spinal cord
sensory nerve
neuron
Brain



Acupuncture
Ca2+
Ion channel activation
Mast cell
Mediators (ATP) release
Positive feedback
Spinal cord
sensory nerve
neuron
Brain

Model 1： a mathematical model of a mast cell



Memberane channel:

MSC\CRAC\PMCA

ER channel:

IP3R\SERCA\LEAK

Species concentration

Ca\IP3\PKC\LTC4

Yao Wei. Huang Huaxiong. Ding Guanghong. A dynamic model of calcium signaling in mast cells and LTC4 release induced by mechanical stimuli. Chinese Science Bulletin. 2014,5(10): 956–963

Equation 1：Memberane channel MSC\CRAC\PMCA

$$I_{Ca,type} = P_{type} \frac{g_{Ca,type} F E_m \left([Ca^{2+}]_i - \exp\left(-\frac{E_m}{\phi} \right) [Ca^{2+}]_e \right)}{\phi \left(1 - \exp\left(-\frac{E_m}{\phi} \right) \right)}$$

$$P_{sti} = \frac{1}{1 + \beta exp(-\tau)}$$

$$P_{CRAC} = \frac{1}{1 + [Ca^{2+}]_{ER} / [Ca]_{act1/2}}$$

$$I_{PMCA} = I_{PMCA,M} \frac{[Ca^{2+}]_i}{K_{PMCA} + [Ca^{2+}]_i}$$

Silva HS. Kapela A. Tsoukias NM. A mathematical model of plasmamembrane electro physiology and calcium dynamics invascularendothelial cells. American Journal of Physiology—CellPhysiology. 2007, 293:277-293.

Equation 2：ER channel: IP3R\SERCA\LEAK

$$J_{Ip3} = J_{max}\left(\frac{IP_3}{IP_3+K_I}\frac{[Ca^{2+}]_i}{[Ca^{2+}]_i+K_{act}}h\right)^3\left(1-\frac{[Ca^{2+}]_i}{[Ca^{2+}]_{ER}}\right)$$

$$J_{pump} = V_{max}\frac{[Ca^{2+}]_i^2}{[Ca^{2+}]_i^2+K_p^2}$$

$$J_{leak} = P_L(1-\frac{[Ca^{2+}]_i}{[Ca^{2+}]_{ER}})$$

Bennett MR. A Quantitative Model of Cortical Spreading DepressionDue to Purinergic and Gap-Junction Transmission in AstrocyteNetworks, Biophysical Journal, 2008, 95: 5648-5660

Equation 3: Species concentration Ca\IP3\PKC

$$\frac{d[Ca^{2+}]_i}{dt} = -\gamma(I_{CRAC} + I_{Ca,MS} + I_{PMCA}) - \gamma \cdot \lambda(J_{Ip3} + J_{leak} - J_{pump})$$

$$\frac{d[Ca^{2+}]_{ER}}{dt} = J_{Ip3} + J_{leak} - J_{pump}$$

$$\frac{d[IP_3]}{dt} = r_h((PIP_2)_T - IP_3) - k_{deg}[IP_3]$$

$$\frac{d[PKC_A]}{dt} = k_{aP}([PKC_T] - [PKC_A])[Ca^{2+}]_i - k_{dP}[PKC_A]$$

Results 1: Memberane currents

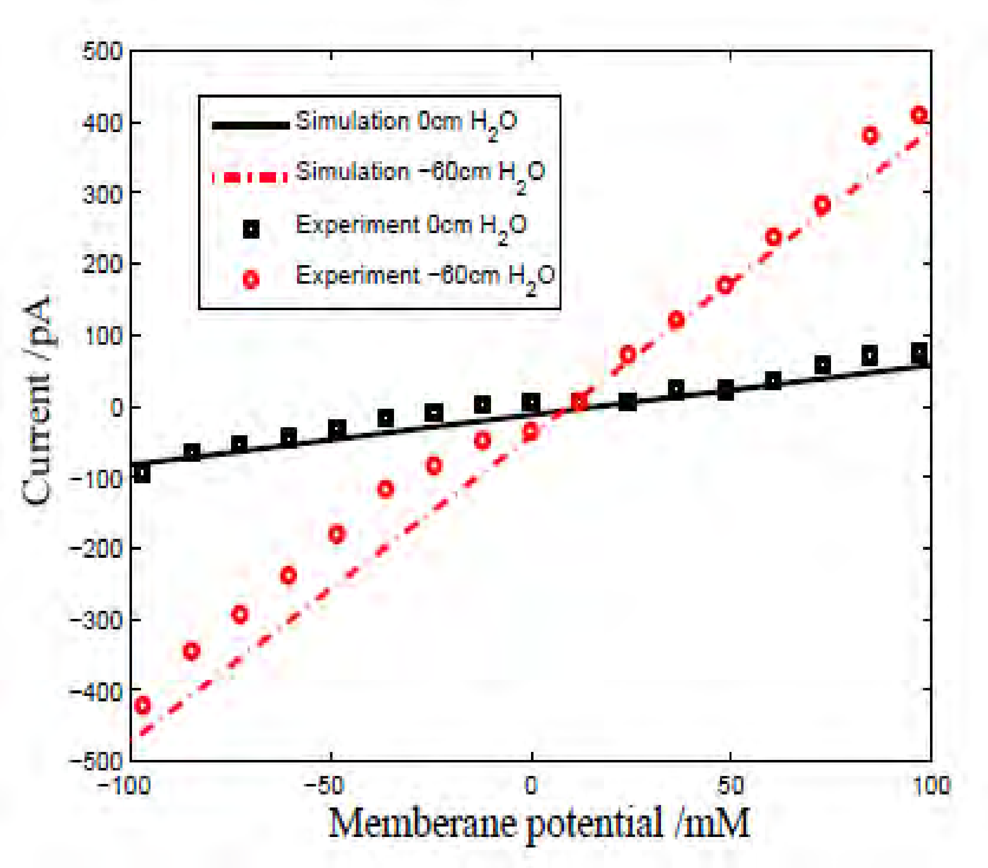


Fig1. Current-Voltage relationships of membrane current induced by different stretch pressures, black solid line represents simulation results without negative pressure stimulation (0cmH2O), red dash line represents simulation results during negativepressure stimulation (-60cm H2O), open square represents the experimental data without negative pressure stimulation (0cm H2O)and open circle represents the experimental data during negative pressure stimulation (-60cm H2O)

Zhang Di, Spielmann A, Ding Guanghong*, Activation of Mast-cell Degranulation by Different Physical Stimuli Involves Activation of the Transient-receptor-potential Channel TRPV2, Physiological research, 2012, 61(1): 113-124

Results 2: Ca signals

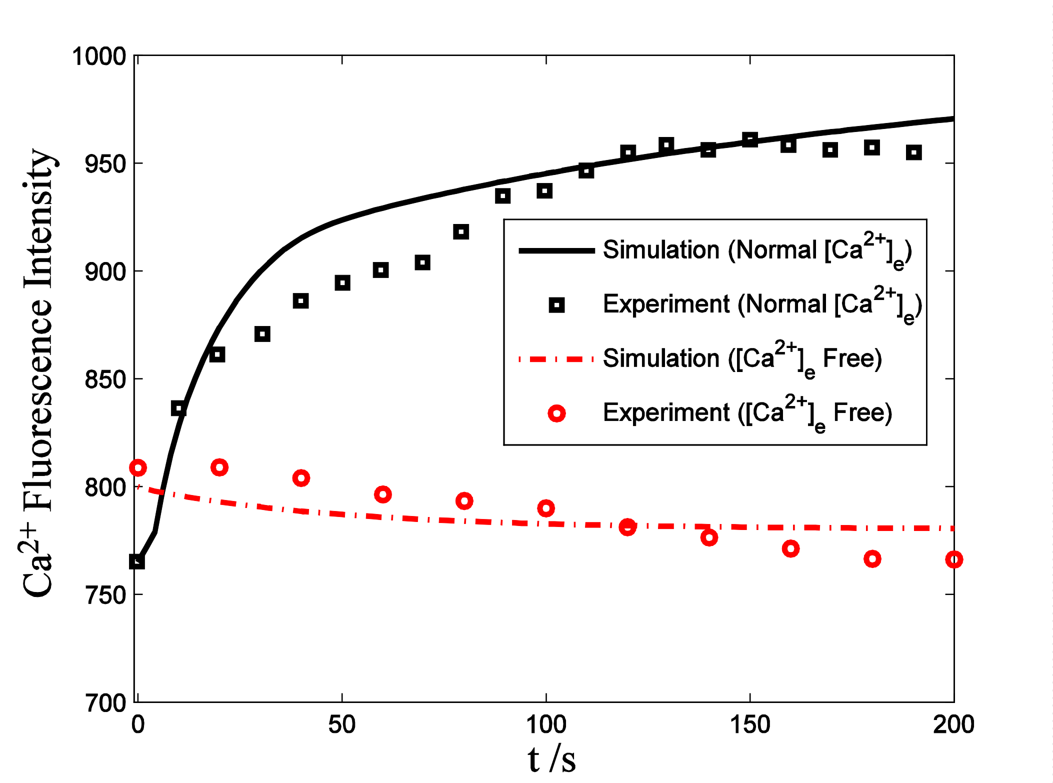
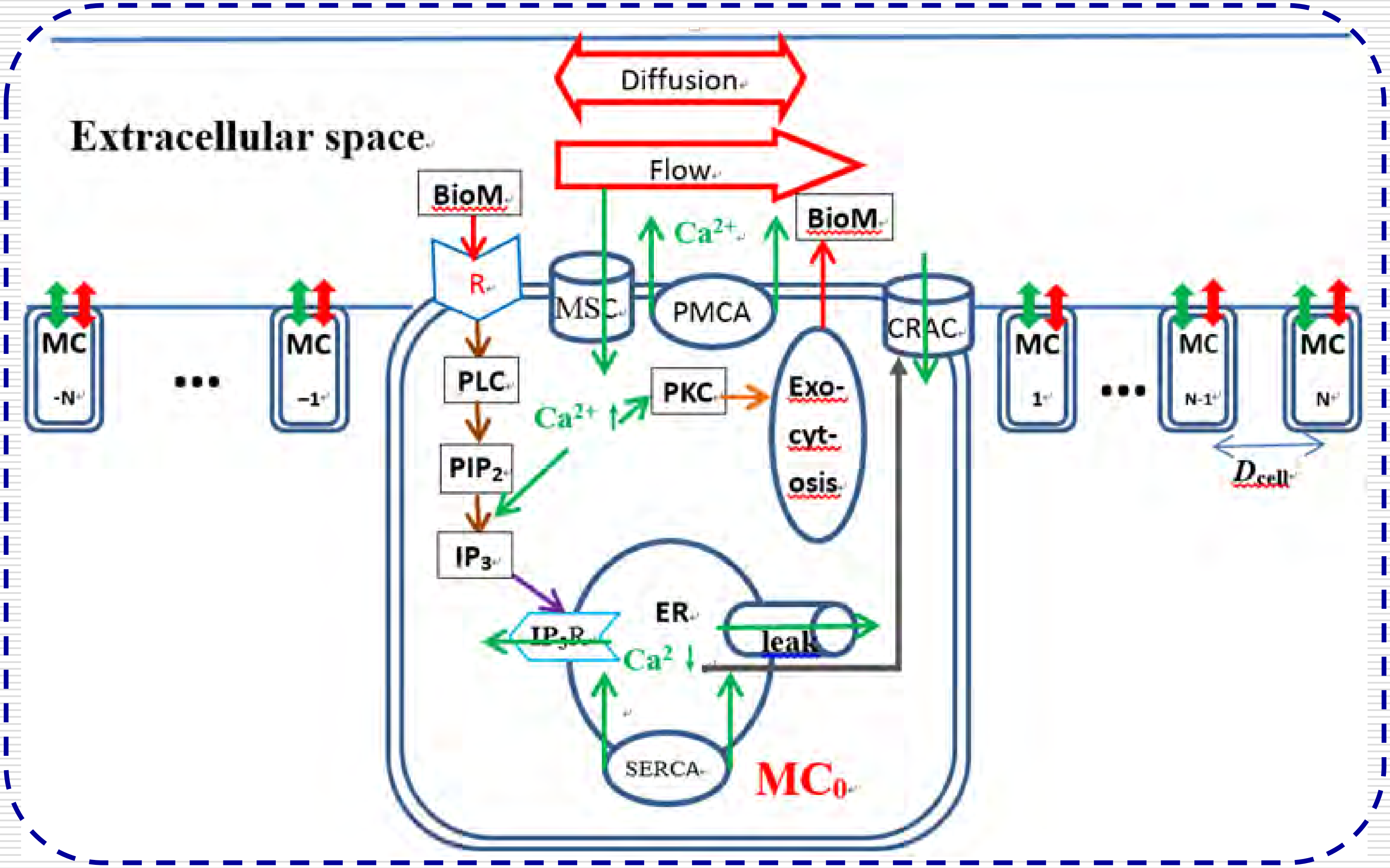


Fig 2. Time-dependent profile of cytosol Ca^{2+} fluorescence intensities in a cell under the stimulation of shear stress. The time 0 represents the beginning of stimulation, open squares represent the experimental data in Hank's buffer ($[Ca^{2+}]_e = 2 \times 10^{-3}$ M), circles represent the experimental data in the Ca^{2+}-free saline ($[Ca^{2+}]_e = 0$ M), solid line represents the simulation results in Hank's buffer and dash line represents the simulation results in the Ca^{2+}-free saline.

Model 2： a mathematical model of mast cells network



Wei Yao Yabei Li and Guanghong Ding. Dynamics of calcium signal and leukotriene C4 release in mast cells network induced by mechanical stimuli and modulated by interstitial fluid flow

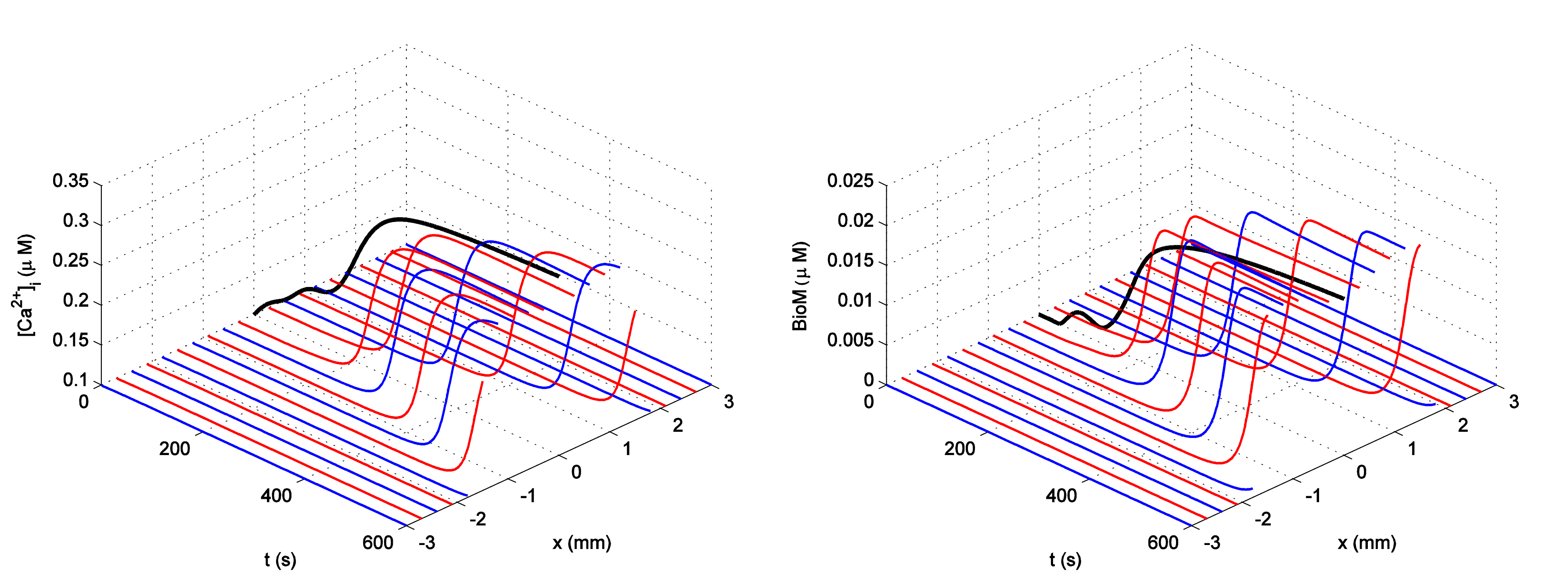
Equation 4: Bio-mediators production, diffusion and convection

Production
$$\frac{d[\mathrm{BioM}]}{dt} = V_{\mathrm{Bio}}\xi \max\{[PKC_A]-[PKC_A]_{min}, 0\}$$

Diffusion
$$\frac{\partial[\mathrm{BioM}]}{\partial t} = D_{\mathrm{Bio}}\frac{\partial^2[\mathrm{BioM}]}{\partial x^2} + [\mathrm{BioM}]_{production}$$

Convection
$$\frac{\partial[\mathrm{BioM}]}{\partial t} = D_{\mathrm{Bio}}\frac{\partial^2[\mathrm{BioM}]}{\partial x^2} - v_{flow}\frac{\partial[\mathrm{BioM}]}{\partial x} + [\mathrm{BioM}]_{production}$$

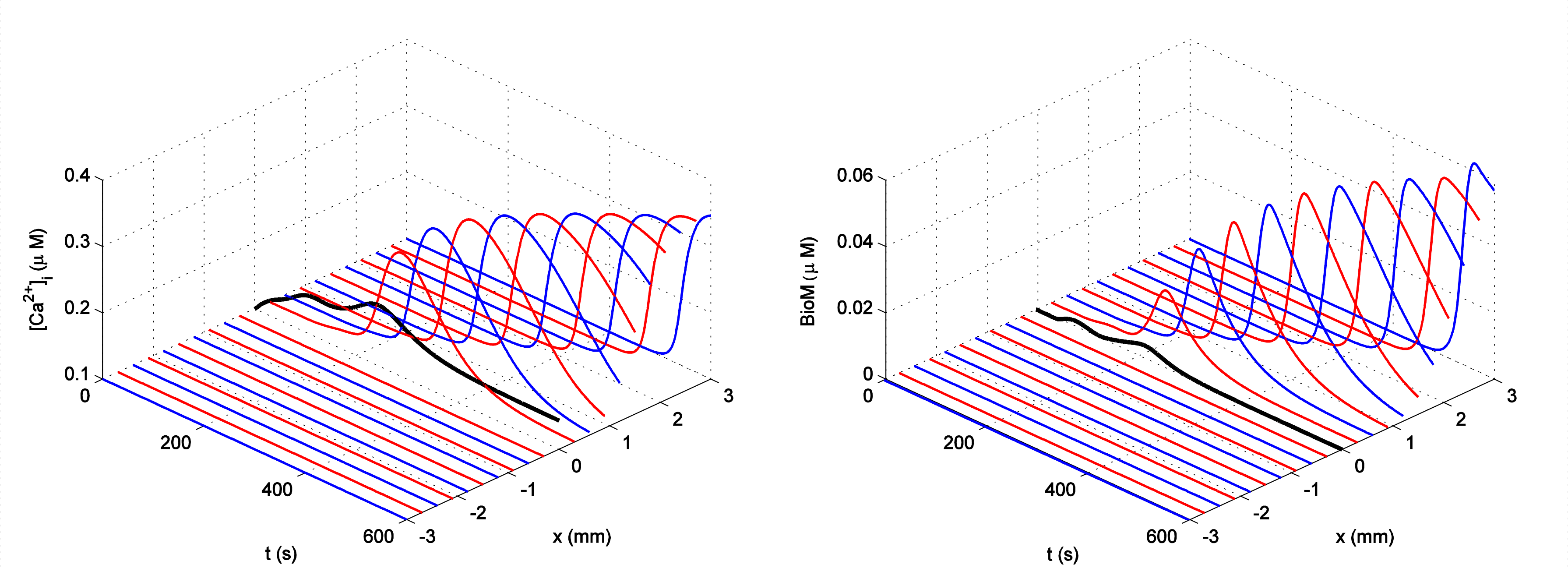
Results 3: Ca and BioM signals (diffusion)



(a) (b)

Fig.3 The response of MCs network of $D_{cell}=3\times10^{-5}$ m to mechanical stimulate at MC_0 (the MC at x=0 position) due to diffusion. (a) cytosol Ca^{2+} propagation, (b) extracellular BioM propagation.

Results 4: Ca and BioM signals (diffusion+convection)



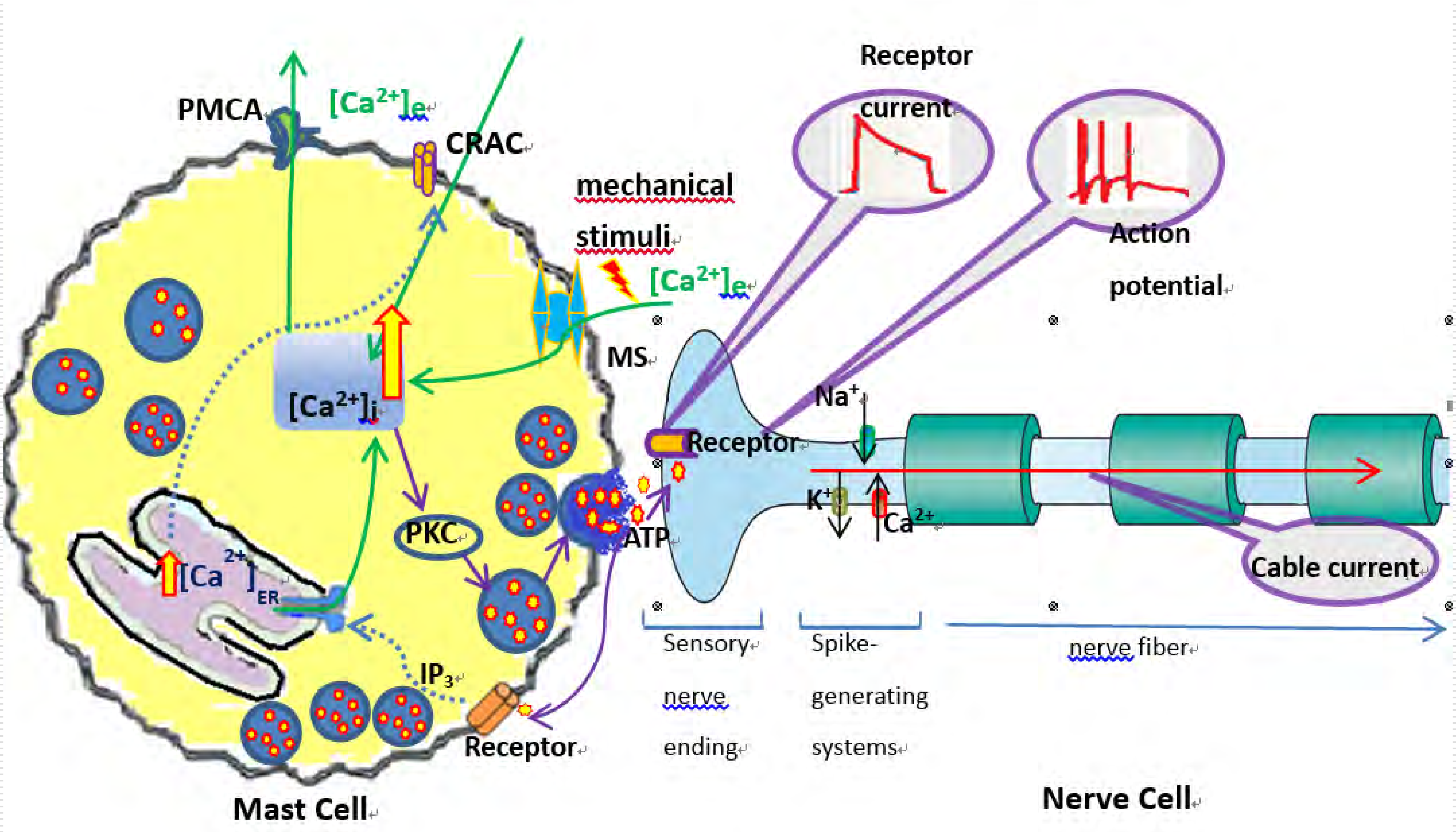
(a) **(b)**

Fig.4 The response of MCs network of 3×10^{-5} m to mechanical stimulate at MC_0 due to diffusion and convection (v_{flow}=5×10^{-6} m s^{-1}). (a) cytosol Ca^{2+} propagation, (b) extracellular BioM propagation.

Results 5：Comparison

Type	D_{cell}	Propagation speed	Ca^{2+} peak
Diffusion & $v_{flow}=0$	3×10^{-5} m	3.37×10^{-6} m s^{-1}	0.30×10^{-6} M
	6×10^{-5} m	2.71×10^{-6} m s^{-1}	0.24×10^{-6} M
	1.5×10^{-4} m	1.85×10^{-6} m s^{-1}	0.16×10^{-6} M
	3×10^{-4} m	No	
Diffusion & $v_{flow}=1\times10^{-6}$ m s^{-1}	3×10^{-5} m	Downstream: 4.03×10^{-6} m s^{-1}	0.32×10^{-6} M
		Upstream: 2.60×10^{-6} m s^{-1}	0.30×10^{-6} M
Diffusion & $v_{flow}=5\times10^{-6}$ m s^{-1}	3×10^{-5} m	Downstream: 6.90×10^{-6} m s^{-1}	0.34×10^{-6} M
		Upstream: No	

Model 3: a mathematical model of mast cell-nerve cell interaction



Yao Wei. Yang Hongwei. Yin Na. Ding Guanghong. Mast Cell-Nerve Cell Interaction at Acupoint: Modeling Mechanotransduction Pathway Induced by Acupuncture. International Journal of Biological Sciences. 2014; 10(5): 511-519.

Equation 5: currents and potential in neurons

Current induced by ATP

$$I_{\mathrm{ATP,ion}} = g_{\mathrm{ATP}} mh \frac{FE_m \left([\mathrm{ion}]_i - \exp\left(-\frac{E_m}{\phi} \right) [\mathrm{ion}]_e \right)}{\phi \left(1 - \exp\left(-\frac{E_m}{\phi} \right) \right)} \frac{[ATP]}{[ATP] + [ATP]_{act1/2}}$$

Memberane Current

$$I_j = \left[g_{Na}(E_{\mathrm{m}} - E_{Na}) + g_K(E_{\mathrm{m}} - E_K) - g_L(E_{\mathrm{m}} - E_L) \right] - I_{ATP,K} - I_{ATP,Na} - I_{ATP,Ca} - I_{L,Ca} - I_{pump}$$

Memberane potential

$$C_m \frac{\partial E_{\mathrm{m,j}}}{\partial t} = -I_j + \frac{d}{4Ra} \frac{E_{\mathrm{m,j+1}} + E_{\mathrm{m,j-1}} - 2E_{\mathrm{m,j}}}{\delta x^2}$$

Results 6： Action potential induced by mechanical stimuli

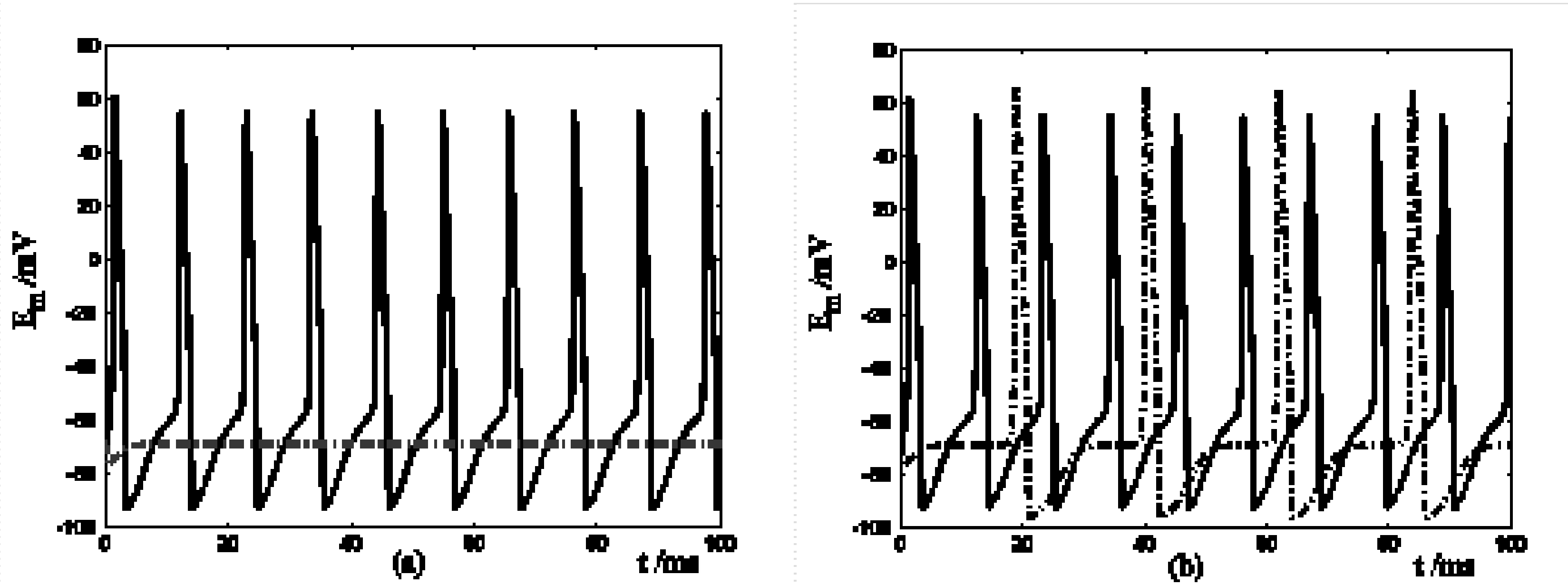


Figure 5 Response of Em in a single isolated nerve cell model to ATP stimuli. Solid line represents simulation results of the segment exposed to an initiating ATP stimuli, dash line represents simulation results of the segment without ATP stimuli. (a) block the cable current from the activated segment to other segment of the nerve cell. (b) include cable current from the activated segment to other segment of the nerve cell.

Results 7： Contours of BioMs and action potentials

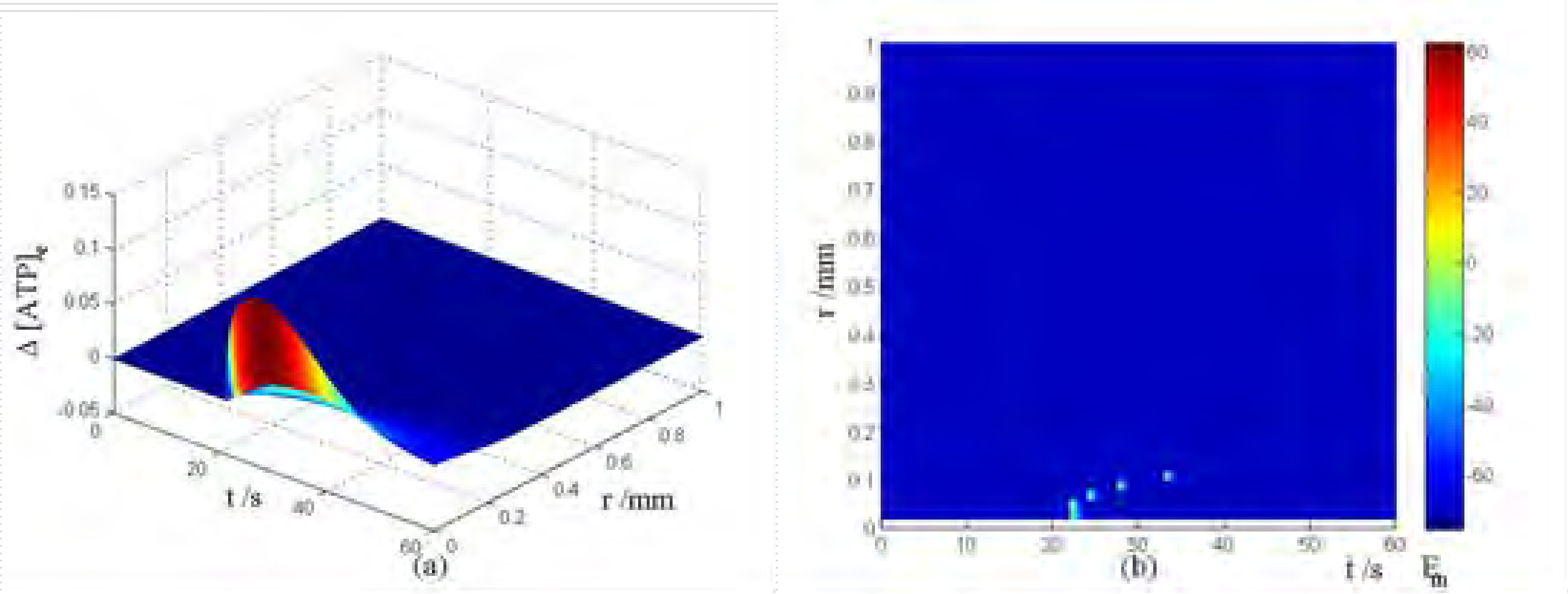


Figure 6 Changes in [ATP]e and [Ca2+]i in the coupled mast cell and nerve cell model, as functions of time (t) and radius distance (r), after its exposure to an initiating mechanical stimuli at r=0 during time t=0−60s. (a) [ATP]e contour in ECS. (b) Em response in nerve cells.

Conclusion

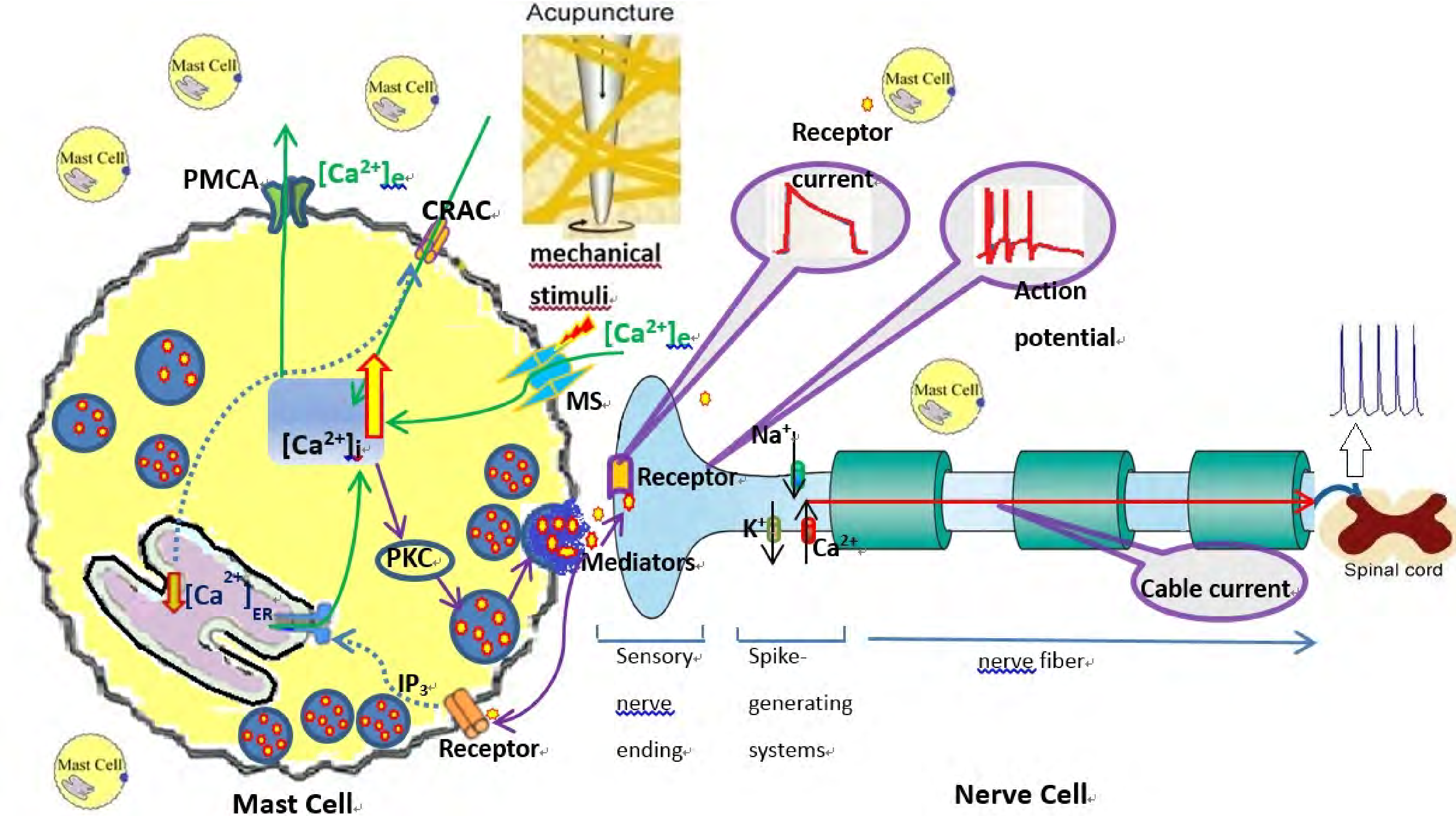
Ⅰ Mechanical stimuli activate signaling pathway coupling MS channels ($TRPV_2$) to Ca^{2+} fluxes and biomedical messengers' release in MCs

Ⅱ Biological responses activated by mechanical stimuli can propagate in MCs network due to diffusion and convection in ECS

Ⅲ The biomedical messengers' release from MCs activate nerve cells and induce signal transporting in neural network.

Ⅳ The interaction of mast cell and nerve cell play a key role in response to mechanical treatment in TCM

Next work： a mathematical model of mast cells and nerve cells network



Thanks！

2014.10