Future of Pain Management

We should think out of box!

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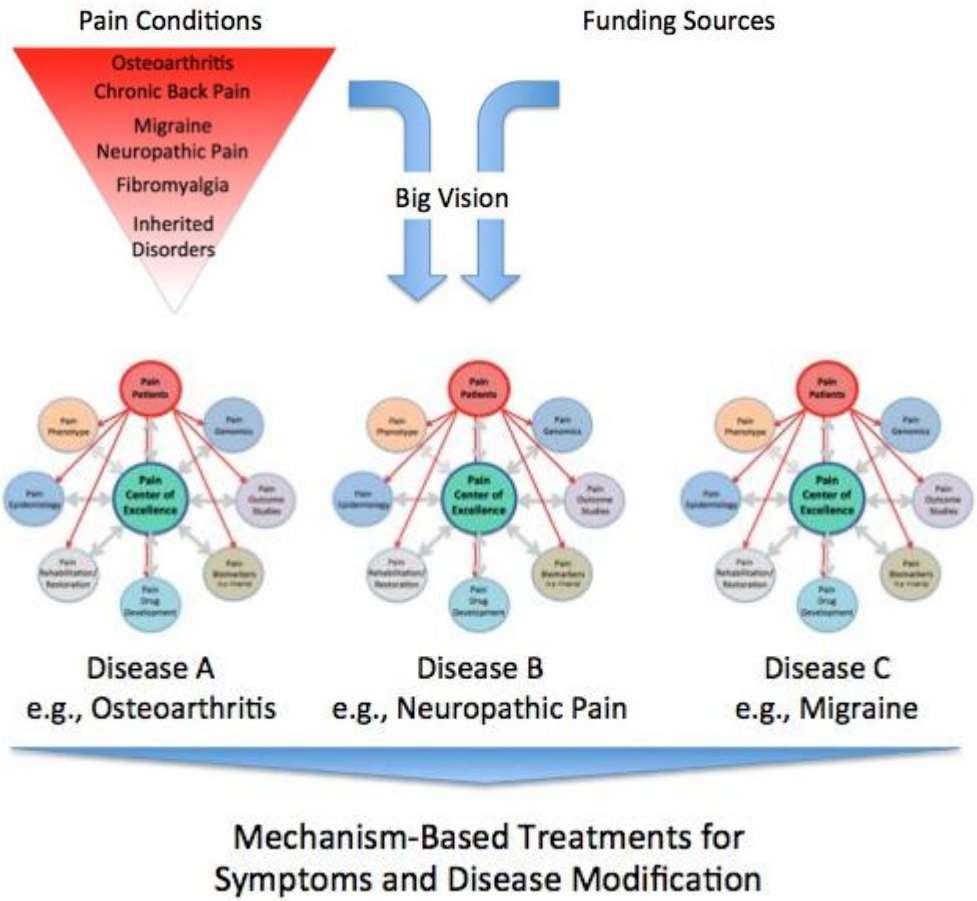

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A Future Without Chronic Pain?

There are several directions:

- Cell-based therapy
- Gene therapy
- Optogenetics
- Technoceuticals
- Drug-free approaches
- New drugs (diverse range)
- Education and self-managements, services (robotics, remote), Apps, etc.

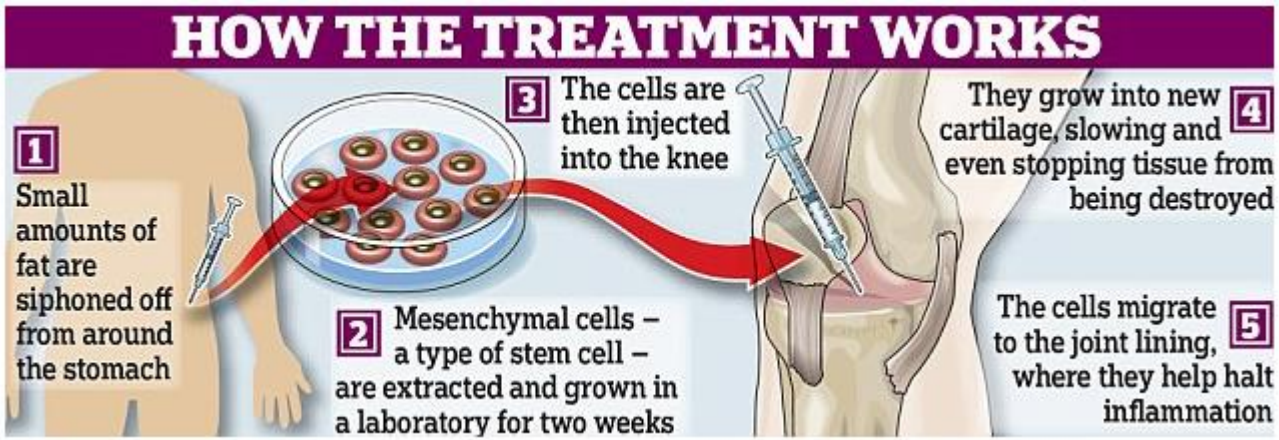
Stem cells

- Since the early 1990s, the topic of stem cells has been a subject of public attention.
- Their ability to restore and repair has made them a beacon of hope in the medical field, especially in terms of diseases like heart disease and Alzheimer's. But they also pose exciting possibilities for chronic pain.
- Stem cells, in a word, are “undifferentiated.” That means that unlike other cells in the body, they have the potential to develop into a wide variety of other cells. They also carry with them the ability to repair and restore internal systems. So, in theory, it’s possible for stem cells to help repair tissues, muscles, blood, bones and organs, aiding growth and possibly even replacing missing pieces!
- Stem cells can be gathered from several locations, including but not limited to bone marrow and adipose (or fat) tissue.
- For the purposes of pain management, cells are collected that may be conditioned in various ways and they’re then injected at the site of the issue, with the hope of helping the affected tissue or system regenerate itself.
- One of the main concerns of utilizing stem cells – and therefore one of the main areas of concentration in scientific studies – is the safety, specifically regarding abnormal cell growth

The Future of Stem Cells for Pain Relief, Posted by Brenda Poppy on Feb 21, 2017

Stem cells in pain

- Due to stem cells' ability to restore and regenerate, their application toward pain management is logical.
- Stem cells are an exciting treatment solution for conditions such as degenerative disc disease and disc herniation. Disc degeneration, which can occur due to aging or injury, causes the discs to weaken and tear, meaning they no longer provided the needed support for the spine. This can result in herniation (a rupture of the disc, which then presses painfully against spinal nerves).
- Not only do stem cells work to reduce the pain and inflammation associated with these conditions, but they also work to repair and regenerate the damaged regions.
- So far, research into the application of stem cells for pain has been positive. Given the anti-inflammatory properties of mesenchymal stem cell (MSC) populations, these cells look attractive in pain research!



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Orozco L, Munar A, Soler R, Alberca M, Soler F, Huguet M, Sentis J, Sanchez A, Garcia-Sancho J: Treatment of knee osteoarthritis with autologous mesenchymal stem cells: a pilot study. Transplantation 2013; 95:1535-41.

https://becomepainfree.files.wordpress.com/2013/01/stem-cell-diagrama.jpg

Cell therapy with brain neural precursors

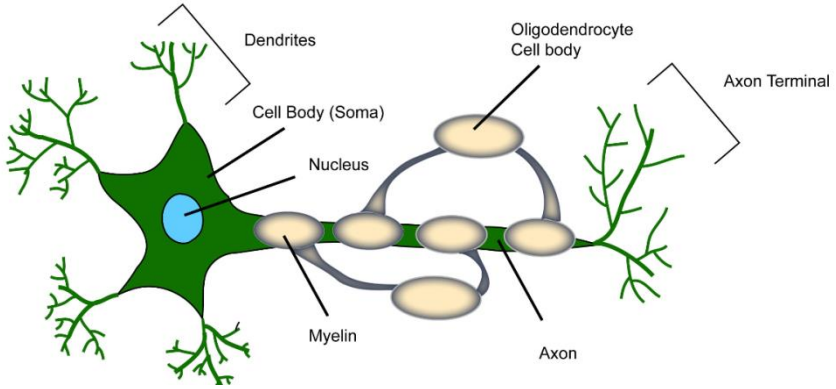
- Neuropathic pain is associated with loss of inhibition via GABAergic interneurons (cells that output the chemical messenger gamma-aminobutyric acid) at the level of the spinal cord.
- A cell therapy approach has directed at replacing the lost inhibitory cells by transplanting mouse embryonic brain neural precursors (destined to become GABAergic neurons) into the spinal cord of mice with pain caused by sciatic nerve injury (a neuropathic pain model).
- The transplanted cells developed into inhibitory neurons, resulting in improvement in pain assessed by mechanical hypersensitivity tests.
- Other studies have reported similar results using pre-differentiated neural progenitors (pushed toward GABAergic fate before transplantation) in the rat sciatic nerve chronic constriction injury model.

Braz JM, Sharif-Naeini R, Vogt D, Kriegstein A, Alvarez-Buylla A, Rubenstien JL, Basbaum AI: Forebrain GABAergic neuron precursors integrate into adult spinal cord and reduce injury-induced neuropathic pain. Neuron 2012; 74:663-75.
Jergova S, Hentall ID, Gajavelli S, Varghese MS, Sagen J: Instraspinal transplantation of GABAergic neural progenitors attenuates neuropathic pain in rats: a pharmacologic and neurophysiological evaluation. Exp Neurol 2012; 234:39-49.

Cell therapy with brain non-neural precursors: Embryonic stem cell-derived oligodendrocyte precursors

- Murine embryonic stem cell-derived oligodendrocyte precursors have also been transplanted. Pre-oligodendrocytes differentiated into more mature oligodendrocytes (glial cells concerned with production of myelin) after transplantation, and mechanical allodynia (hypersensitivity) is reduced in a murine model of laminectomy as a function of transplantation.

- Another study has used this for treating acute thoracic spinal cord injury in a short-lived phase I clinical trial using human embryonic stem cell-derived pre-oligodendrocytes



Tao F, Li Q, Liu S, Wu H, Skinner J, Hurtado A, Belegu V, Furmanski O, Yang Y, McDonald JW, Johns RA: Role of neuregulin-1/ErbB signaling in stem cell therapy for spinal cord injury-induced chronic neuropathic pain. Stem Cells 2013; 31:83-91.

Lukovic D, Stojkovic M, Moreno-Manzano V, Bhattacharya SS, Erceg S: Perspectives and future directions of human pluripotent stem cell-based therapies: lessons from Geron's clinical trial for spinal cord injury. Stem Cells Dev 2014; 23:1-4.

Oligodendrocytes are the myelinating cells of the central nervous system (CNS

Summary - stem cell therapy

Pain Physician 2017; 20:293-305 • ISSN 1533-3159

Narrative Review

Stem Cell Therapy for Chronic Pain Management: Review of Uses, Advances, and Adverse Effects

Krishnan Chakravarthy, MD, PhD[1,3], Yian Chen, MD[2], Cathy He, MD[2], and Paul J. Christo, MD[2]

There are a number of ongoing clinical trials involving degenerative disease of the spine, joints, and neuropathic pain and mixed conditions that reflect multiple clinical areas of interest. The majority of ongoing studies are early stage, Phase I or II clinical trials that explore safety and efficacy.

Results from prior studies have been promising for the use of stem cells as a novel therapeutic strategy for discogenic pain, neuropathic pain, and osteoarthritis, additional clinical studies will be needed to validate the benefit of the technology for clinical use.

Current clinical trials both in the United States and internationally.

Location	Modality	Cell Type	Indication	Clinical Trial ID	Enrollment	Phase (if applicable)
USA	Allograft			NCT01771471	Active, not recruiting	Phase II, DB
USA	Allograft	MPC	Lumbar back pain	NCT01290367	Ongoing, not recruiting	Phase II, DB
USA	Autologous	Adipose stromal cell	DJD	NCT02097862	Actively recruiting	NR, Open Label
Spain	Allogeneic	BM MSC	DDD	NCT01860417	Ongoing, not recruiting	Phase I, DB
Austria/Germany	Autologous	Chondrocytes (IVD?)	DJD, herniation	NCT01640457	Actively recruiting	I/II Open Label, Randomized
Korea	Autologous	Adipose MSC	DJD	NCT01643681	Active recruitment	Phase I/II Non-Randomized, Open Label
Egypt	Autologous	MSC	Diabetic neuroapthy	NCT02387749	Ongoing, not recruiting	Phase II/III Open Label, Single Group Assignment
USA	Autologous	MSC	DJD	NCT02529566	Enrolling, Invitation only	Observational, Cohort
Korea	Autologous	Peripheral blood SC	Diabetic neuropathy	NCT02315235	Actively recruiting	Single Blind, Randomized
India	Autologous	Bone marrow SC	Osteoarthritis	NCT01152125	Enrollment by invitation	Phase I/II Open Label, Single Group Assignment
Korea	Autologous	Adipose MSC	Rotator Cuff Disease	NCT02474342	Recruiting	Open Label, Single Group
USA	Autologous	BM aspirate	Knee Osteoarthritis	NCT01931007	Ongoing, not recruiting	Phase I Randomized, Single Group
USA	Autologous	Adipose MSC	Osteoarthritis	NCT02241408	Recruiting	Observational, Cohort
USA	Autologous	Fat grafting	Amputation stump pain	NCT01645722	Ongoing, not recruiting	Open Label, Efficacy
Iran	Autologous	BM stem cell	Knee OA	NCT00550524	Enrolling by invitation	Phase I, Open Label, NR
USA	Autologous	Adipose-derived MSC	Knee OA	NCT01739504	Recruiting	Phase I/II, Open Label, Single Group Assignment
Vietnam	Autologous	Tissue scromal vascular fraction	Knee OA	NCT02142842	Ongoing, not recruiting	Phase I/II, Single Blind, Single Group
Spain	Autologous	MSC	Knee OA	NCT02123368	Ongoing, not recruiting	Phase I/II, Open Lavel, Randomized
China	Autologous	Adipose MPC	Knee OA	NCT02162693	Ongoing, not recruiting	Phase II, Randomized, Single Blind
Canada	Autologous	MSC	Knee OA	NCT02351011	Currently recruiting	Phase I/II Open Label, Non-Randomized

Is there a 'pain gene'?

- A pain gene has been described as: "a gene for which there are one or more polymorphisms that affect the expression or the functioning of its protein product in a way that affects pain response".
- Pain genes are discovered by:
  - Study of large families termed 'linkage analysis'
  - Study of large cohorts of matched, but unrelated, individuals with and without the condition – known as 'association analysis'.
  - Study pain behavior in twins

Summary of genes and effect on pain/analgesia.

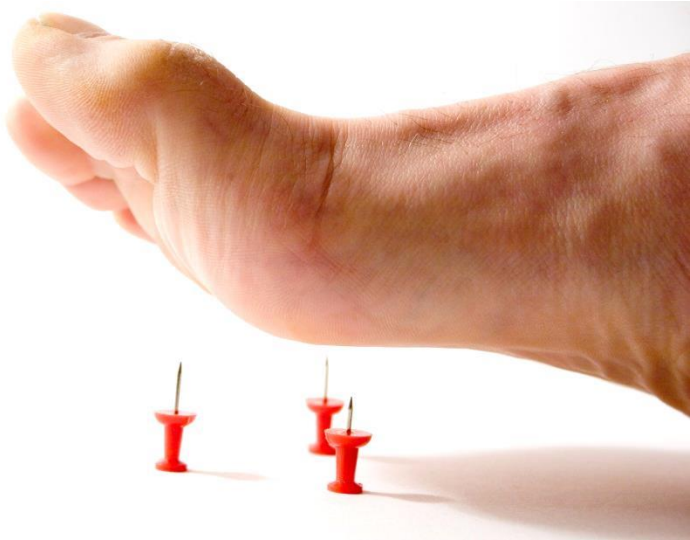
Genes facilitating/ amplifying pain	Genes which confer protection/decrease in pain	Genes involved in the modulation of analgesic efficacy
KCNS1	*COMT*	*COMT*
SCN9A	*OPRM1*	*MC1R*
ADRB2	*TRPV1*[a]	*OPRM1*
H2TRA	*MC1R*	*CYP2D6*
CACNG2	*GCH1*	*ABCB1*
IL16	*CACNA2D3*	

KCNS1: voltage-gated potassium channel; *H2TRA*: serotonin; *ADRB2*: β 2 subtype adrenergic receptor; *COMT*: catechol-*O*-methyl transferase; *MC1R*: melanocortin receptor; *GCH1*: GTP cyclohydrolase.
[a]TRPV1: the 1911 A>G polymorphism was significantly associated with altered heat pain thresholds.

Insensitivity to pain

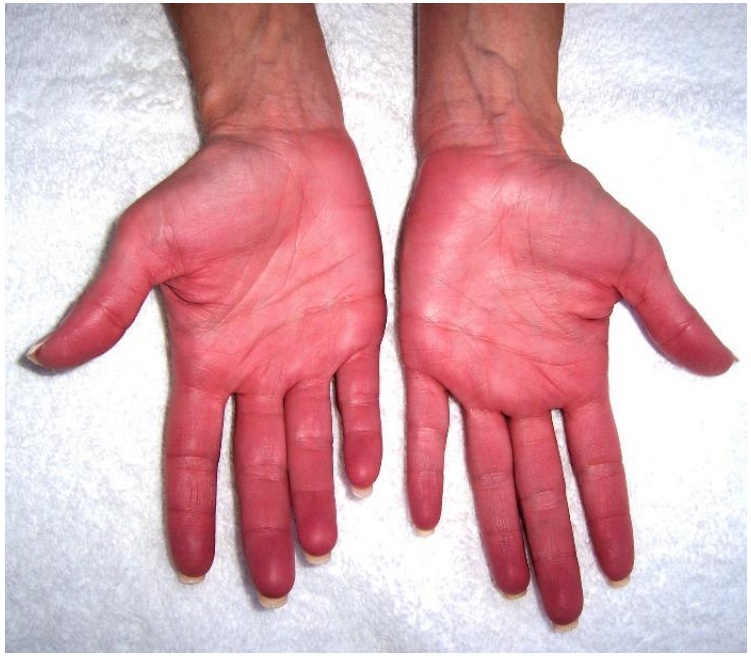
This is inherited as a loss of function in Nav1.7 channel, resulting in a *congenital insensitivity to pain*. The gene affected is the SCN9A gene.

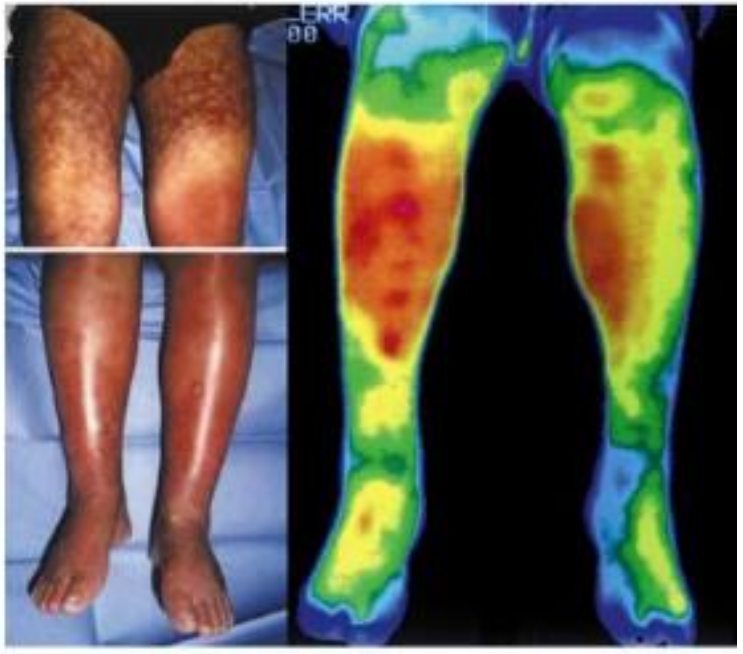
Documentarian Melody Gilbert follows the daily lives of three girls -- a 3-year-old Minnesotan, a 7-year-old Norwegian and a 10-year-old German -- who share an extremely rare disease: congenital insensitivity to pain. Despite the efforts of their vigilant parents, these girls live in constant threat of bodily injury. This moving film was an official selection of the 2005 South by Southwest festival and was featured on "The Oprah Winfrey Show."



Amplification of pain

- **Primary erythromelalgia (formerly known as Mitchell's disease):**
  - a ‘chronic inflammation/burning pain due to a gain-of-function’ mutation of Nav1.7 channel.
  - This disorder appears with symptoms typically including episodes of burning pain and erythema, primarily in the extremities, triggered by exercise or heat.
  - The gene affected is the SCN9A gene.





Genotype-phenotype association in pain

- Researchers have found that red hair is associated with resistance to anesthetics and also to increased anxiety

- MC1R (melanocortin 1 receptor) gene variation, in redheads, makes the nervous system modulate pain more intensely. It's also possible that in redhead the MC1R gene directly affects hormones that stimulate pain receptors in the brain.

- In a study involving 58 pregnant women -- 24 with dark-colored eyes and 34 with light-colored eyes -- those with lighter eyes achieved greater reductions in postpartum anxiety, depression, and catastrophizing/rumination

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Somatosensory & Motor Research

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Individuals with dark eyes and hair exhibit higher pain sensitivity

Henrik Holmgaard, Eva Ørsnæs Hansen, Nhung Phuong Thi Dong, Laila Brøns Dixen, Gebbie Ann Rodriguez Nielsen, Jeppe Nørgaard Poulsen & Parisa Gazerani

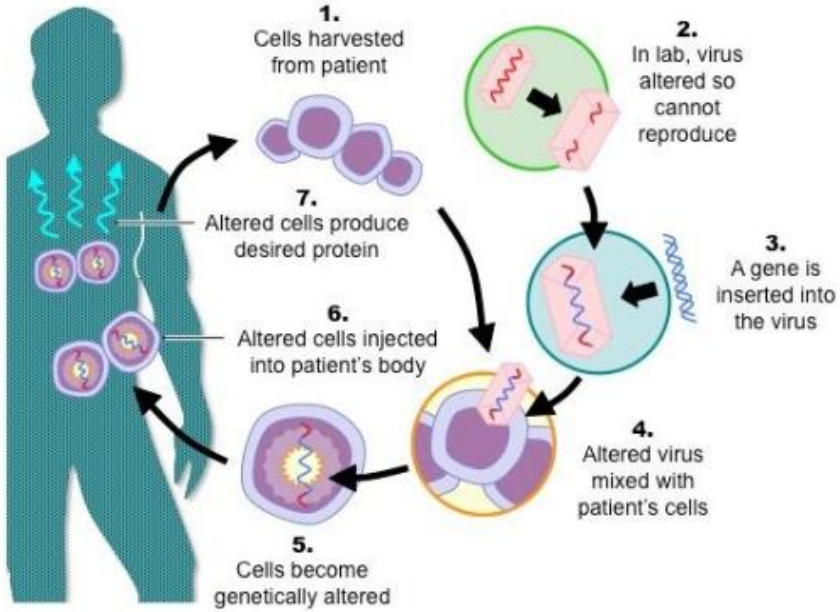
Advances in gene therapy for pain

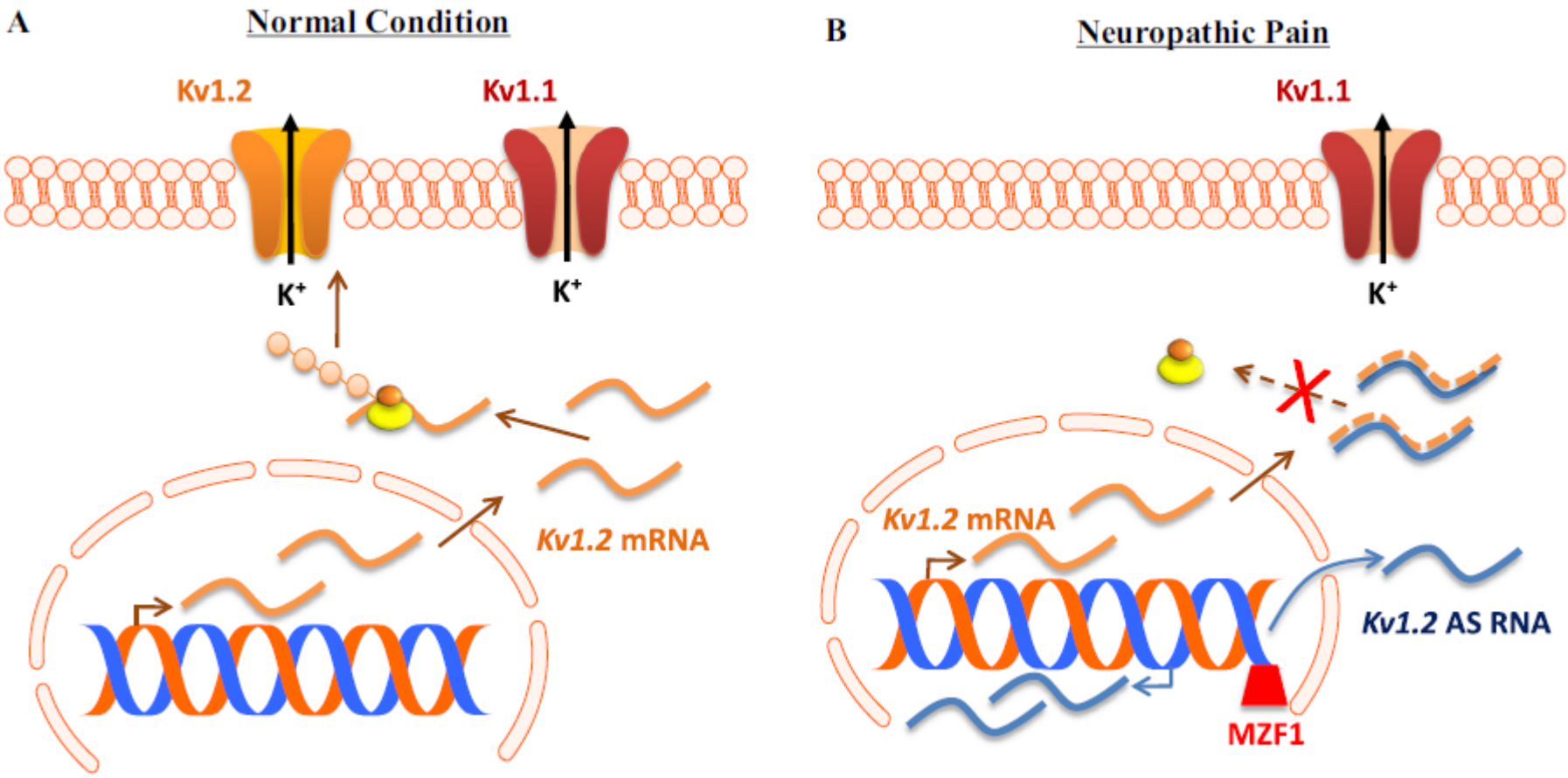
- Pain treatment with gene(s) is unique – it might involve initiating ‘de novo’ expression of an ‘anti-nociceptive’ gene that is not normally present in the target cell or, decreasing the expression of an active ‘pro-nociceptive’ gene in those cells.

- Gene therapy for pain still remains in its infancy but:

  - Novel experimental therapies using viral vectors, including adenoviral, adeno-associated viral, lentiviral and herpes simplex virus (HSV) vectors have been tried.

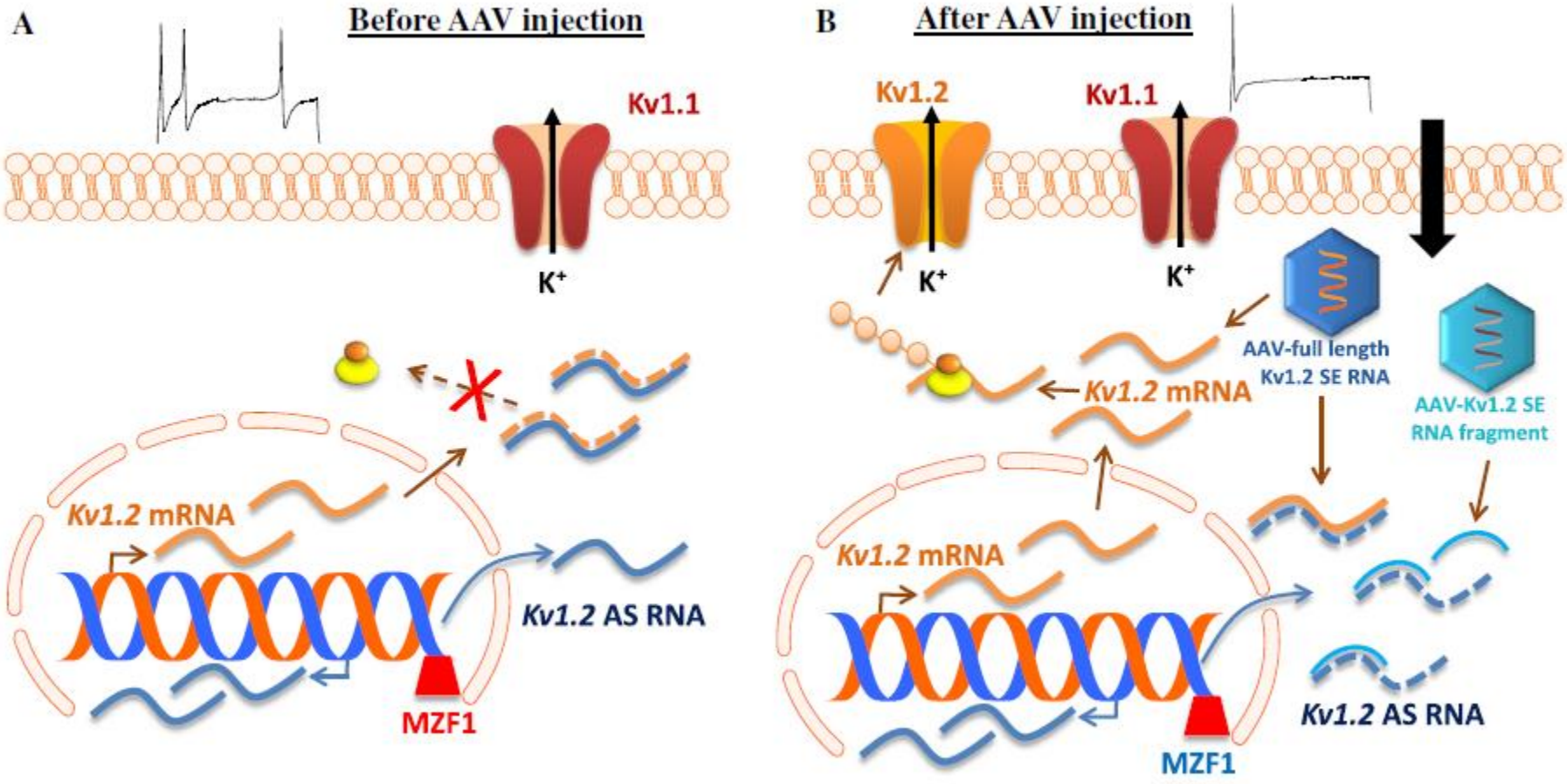
  - Gene therapy–based approaches to treat neuropathic, and cancer pain have been tried.





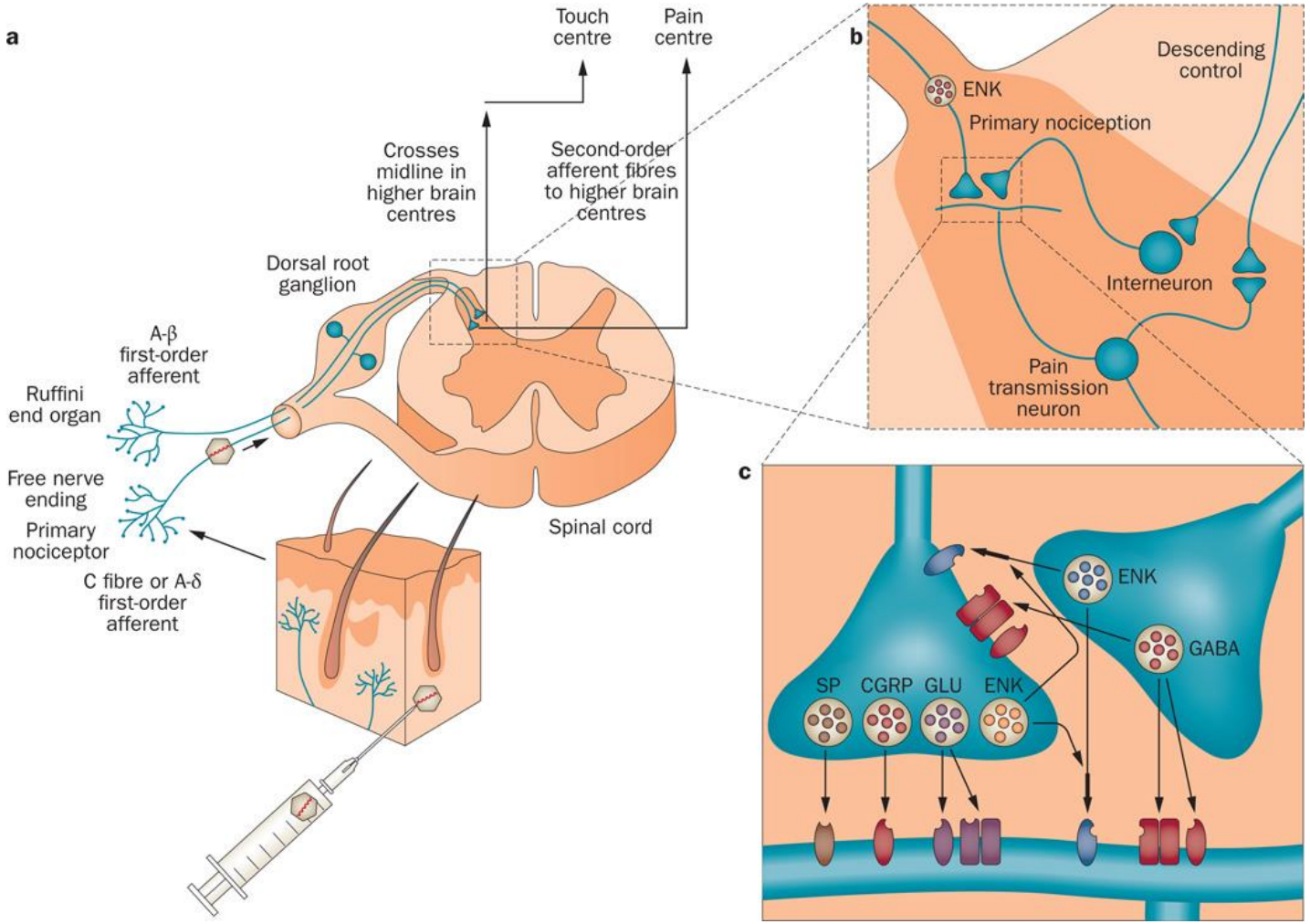
Nerve injury-induced Kv1.2 downregulation triggered by myeloid zinc finger protein 1 (MZF1)-mediated Kv1.2 antisense (AS) RNA expression in the injured dorsal root ganglion (DRG). (A) Under normal conditions, Kv1.2 mRNA that is transcribed from the genome is translated into Kv1.2 protein, resulting in normal expression of Kv1.2 channel at DRG neuronal membrane. (B) Under neuropathic pain conditions, peripheral nerve injury promotes the expression of the transcription factor MZF1 in DRG. The increased MZF1 binds to the promoter region of Kv1.2 AS RNA gene and triggers its expression. The latter specifically and selectively inhibits the expression of Kv1.2 mRNA via extensive overlap of their complementary regions, leading to a reduction in the membrane expression of Kv1.2 only, not other Kv subunits (e.g., Kv1.1), in the DRG neurons.

Guedon et al. Molecular Pain (2015) 11:27



Adeno-associated virus (AAV) mediated transfer of Kv1.2 sense RNA for the reduction of DRG neuronal excitability. (A) Before AAV injection into the DRG of rats with peripheral nerve injury, a nerve injury-induced increase in DRG Kv1.2 AS RNA triggered by MZF1 knocks down expression of Kv1.2 mRNA and protein, resulting in an increase in DRG neuronal excitability under neuropathic pain conditions. (B) After AAV injection into the DRG of rats with peripheral nerve injury, AAV mediated transfer of full length Kv1.2 sense (SE) RNA rescues nerve injury-induced DRG Kv1.2 downregulation at the DRG neuronal membrane through not only its direct translation into Kv1.2 protein but also its indirect blockage of nerve injury-induced increase in Kv1.2 AS RNA expression via extensive overlap of their complementary regions. AAV mediated transfer of Kv1.2 SE RNA fragment (-311 to +40) also rescues nerve injury-induced DRG Kv1.2 downregulation through its blockage of nerve injury-induced increase in Kv1.2 AS RNA expression via partial overlap of their complementary regions, although this RNA fragment cannot be translated into Kv1.2 protein. Maintaining normal Kv1.2 expression at DRG neuronal membrane reduces nerve injury-induced neuronal hyperexcitability at DRG neurons and consequently decreases spinal central sensitization, resulting in neuropathic relief.

Guedon et al. Molecular Pain (2015) 11:27



Gene therapy for pain using an HSV vector. a,b | Pain signalling is mediated by primary sensory afferents that connect via synapses in the spinal cord to release neurotransmitters and peptides, including glutamate, substance P and CGRP. After injection into the skin, the HSV vector is delivered to the cell bodies of primary afferents by retrograde axonal transport, enabling production and release of the transgene product (in this case ENK) from nerve terminals in the dorsal horn. c | ENK released from the transduced primary afferents inhibits nociceptive neurotransmission through binding to opioid receptors at presynaptic and postsynaptic sites Abbreviations: CGRP, calcitonin gene-related peptide; ENK, enkephalin; GAD, glutamic acid decarboxylase; GLU, glutamate; HSV, herpes simplex virus; SP, substance P.

Nat Rev Neurol. 2013 May ; 9(5): 277–291


TIME FOR A BREAK

Optogenetics

SPECIAL REPORT

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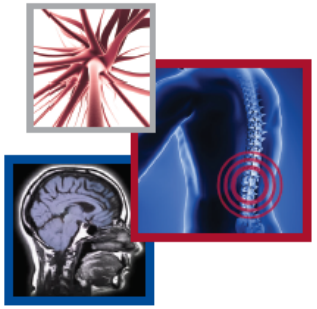
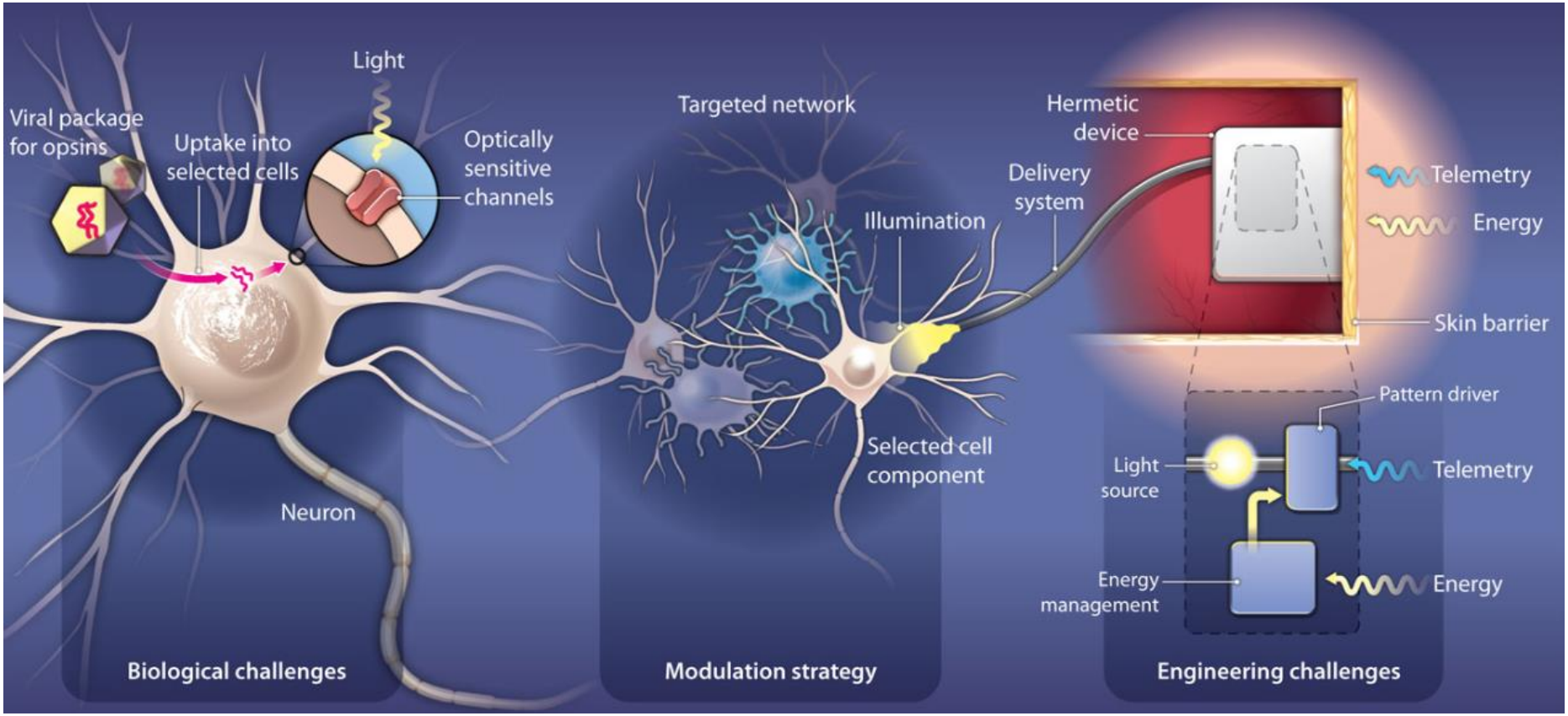
Will optogenetics be used to treat chronic pain patients?

Hélène Beaudry[‡1,2,3], Ihab Daou[‡1,2], Alfredo Ribeiro-da-Silva[2,3] & Philippe Séguéla[*1,2]

Pain Management

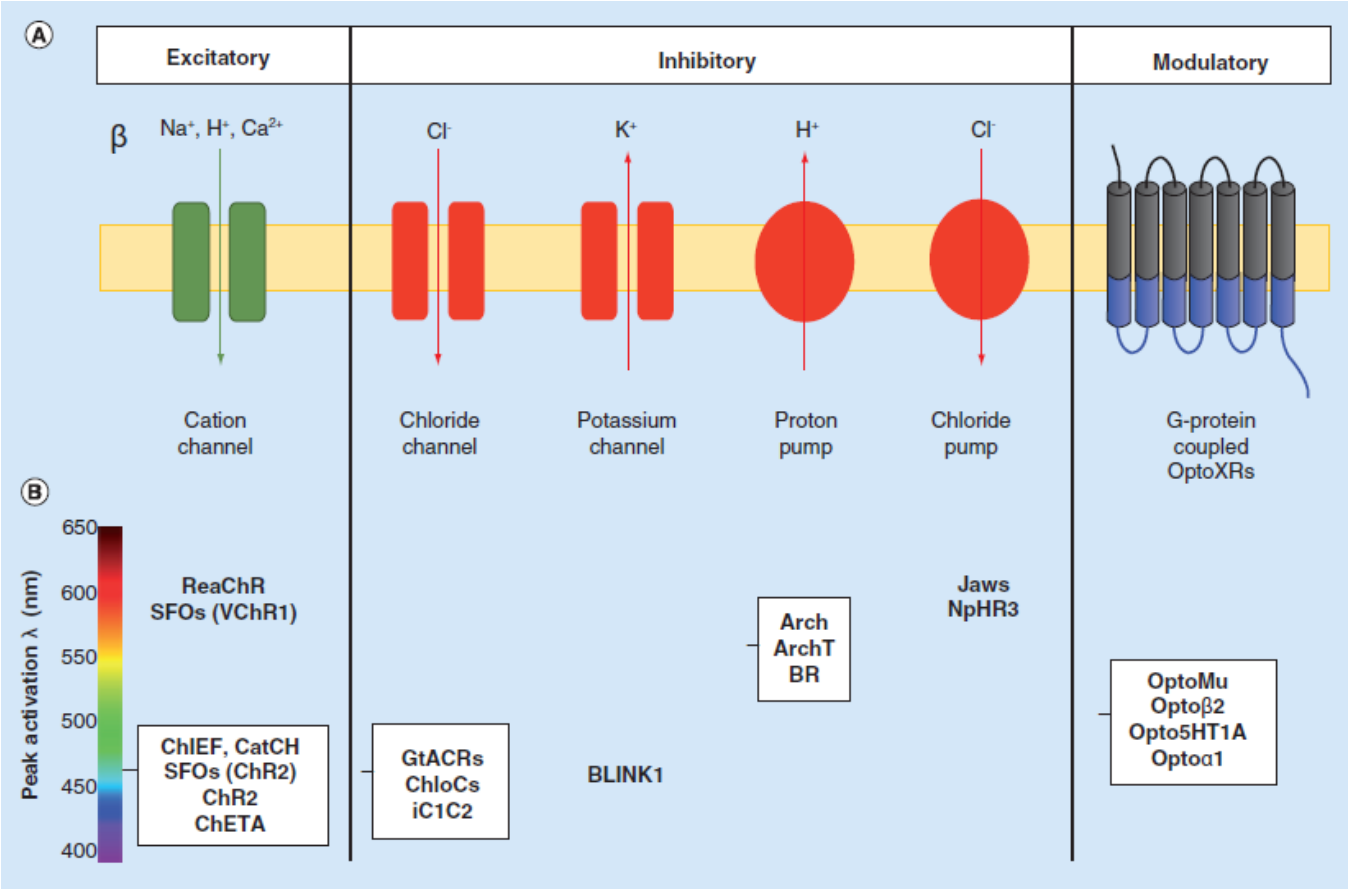


- Optogenetics consists of using genetically encoded and optically active proteins to control signaling events within specific cell types.
- Optogenetics allows high spatial and temporal precision in the regulation of neuronal activity.
- Opsins represent single-component photosensitive proteins that play the role of both light sensors and current generators.
- The noninvasive modulation of a genetically defined cellular population with light limits off-target side effects, an advantage over most pharmacological approaches.
- Evidence from animal models shows that optogenetics is an efficient approach to alleviate inflammatory and neuropathic pain.
- Analgesia by phototherapy would present a promising strategy to treat chronic pain.

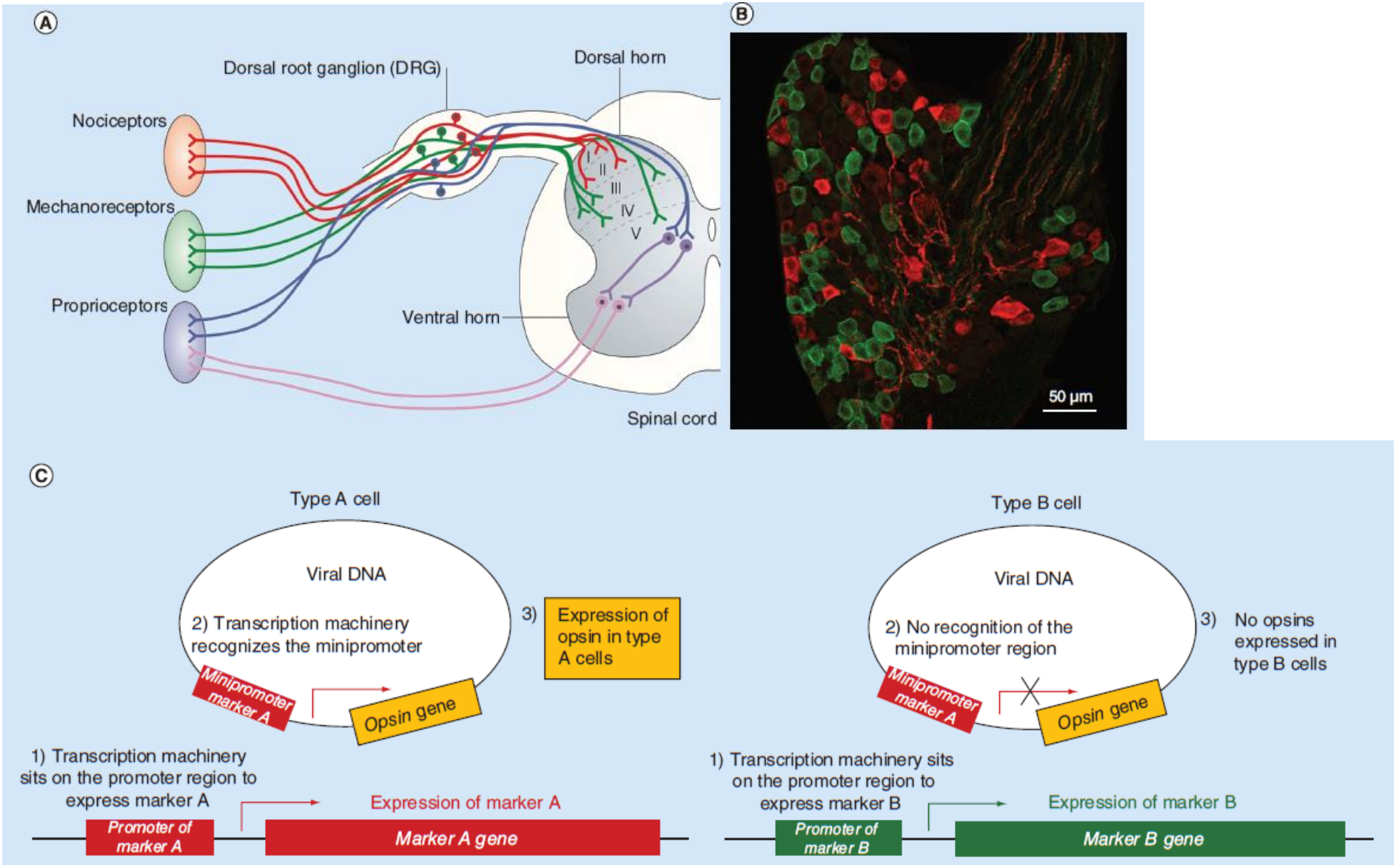


The idealized optogenetic neuromodulation system. An envisioned neuromodulation system based on optogenetic technologies would be multifaceted, including viral or cell-based therapy, fluidic delivery, optical delivery, power, and telemetry.

Classification summary of major optogenetic tools



(A) Opsins are optogenetic actuators that can be categorized into activators, inhibitors or modulators. Most excitatory opsins are nonselective cation channels whereas inhibitory opsins are hyperpolarizing channels (chloride or potassium) or pumps (proton or chloride). OptoXRs are chimeric receptors between a rhodopsin and another GPCR (opioidergic, adrenergic or serotonergic). Optical activation of OptoXRs recruits specific modulatory G protein-dependent and/or G protein-independent intracellular signaling pathways. (B) Main opsins in each category extensively used at the time of writing (2016) with their peak wavelength of activation (λ).



Strategy for selective genetic targeting of highly diverse sensory neuron populations. (A) The cell bodies of primary somatosensory afferents are grouped in dorsal root ganglia with high functional and genetic heterogeneity. (B) A complete segregation of peptidergic CGRP+ (in red) and nonpeptidergic MrgD+ nociceptors (in green, by transgenic expression) is observed in mouse DRG, highlighting two genetically distinct neuronal subsets playing different sensory roles. This heterogeneity is a useful substrate to optogenetically target specific neuronal populations involved in chronic pain. (C) A promoter is a specific DNA sequence that drives the transcription of a gene of interest. Using a virus containing an artificial minipromoter for the Marker A gene upstream of an opsin gene, expression of the opsin will only occur in type A cells expressing Marker A. The transcription machinery in a type B cell would not recognize the minipromoter for Marker A provided by the virus. DRG: Dorsal root ganglia.

Method of the year 2010

https://www.youtube.com/watch?v=LOTsXDYdnv4 4:26 min

The critical issues of penetrance of viral transduction, validation of promoters, effectiveness of light-evoked opsin-mediated modulation, duration of opsin expression as well as induction of immune responses will have to be solved in preclinical models in order to assess the translatability of optogenetics to chronic pain patients.

EDITORIAL

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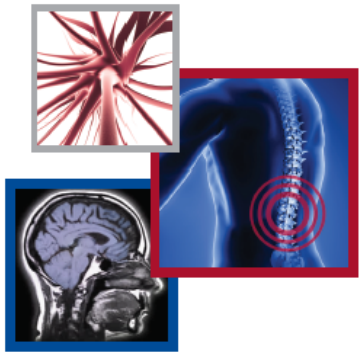


Shedding light on photo-switchable analgesics for pain

Parisa Gazerani*

"Photo-pharmacology deals with a delicate process of design, synthesis and application of drugs that can be modulated with light. This approach offers a possibility to solve off-target side effects."

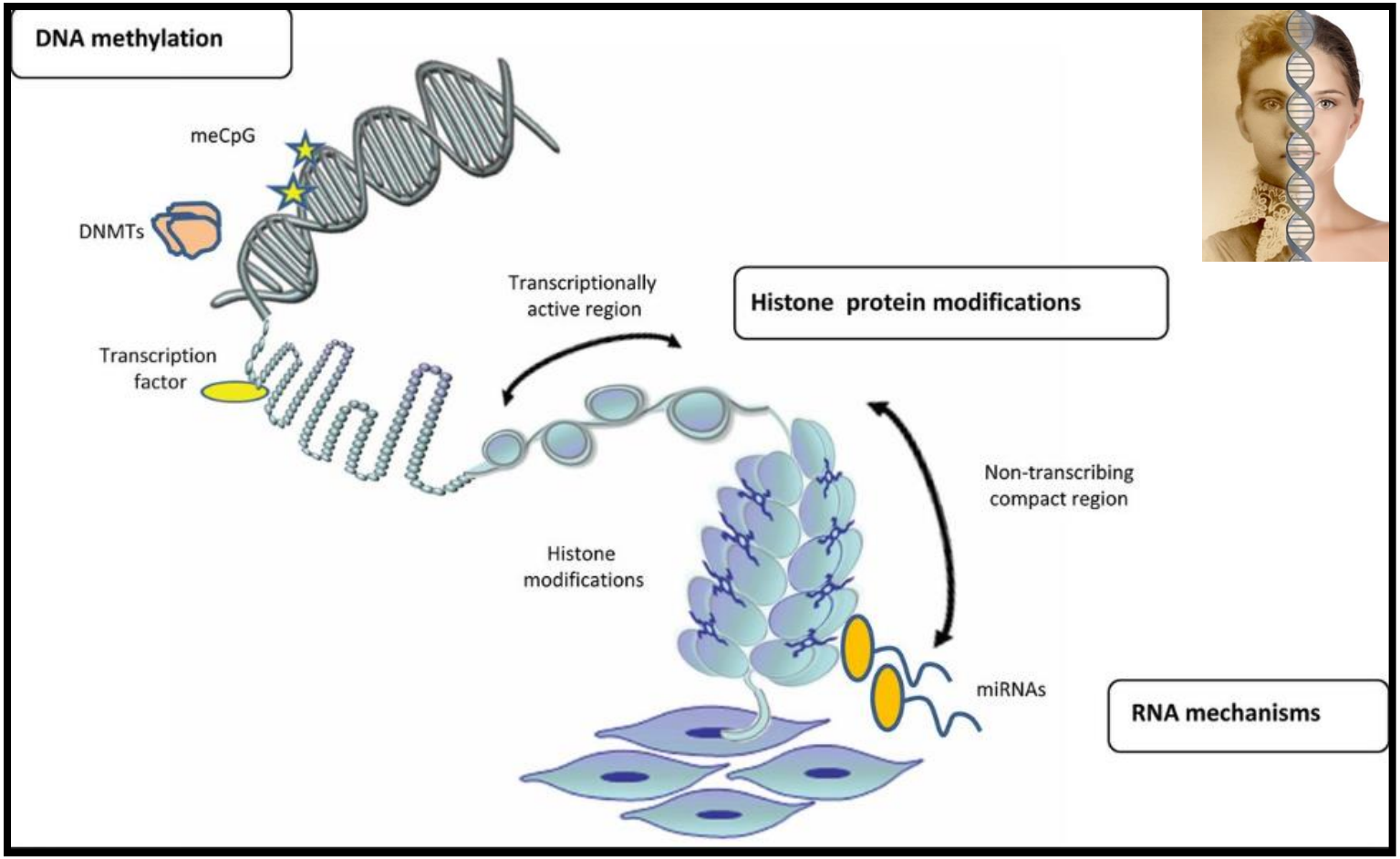
Photo-pharmacological control of nociception is a rapidly growing field. Some photo-switchable compound are already available, but more photo-switchable compounds are in pipeline, for example, for ionotropic glutamate receptors, kainate receptors, AMPA receptors, metabotropic glutamate receptors, adrenergic receptors, muscarinic acetylcholine receptors, dopamine, histamine, serotonin receptors, calcium and potassium channels and number of transporters and pumps. Under ideal conditions, a photo-switchable compound is active as an agonist or antagonist in one molecular structure and fully inactive in other. Besides delivery issues, testing and ensuring efficacy and safety of developed compounds, economic aspects of development must also be taken into account for further development of realistic choices toward their clinical use.

Pain Epigenetics

- The term Epigenetics is used to describe the link between the ‘gene’ and the ‘environment’.
  - Factors implicated are age, nutrition, environmental chemicals, social context and so on.
- There is growing evidence that epigenetic mechanisms can modulate the expression of pro- or anti-nociceptive genes.
- Processes such as histone modifications and DNA methylation have been known to be associated with altering many neural functions, including synaptic plasticity, memory and learning.
- Epigenetic mechanisms have also been implicated in the transition from acute to chronic pain, development of chronic post-surgical neuropathic pain, human bladder pain syndrome and primary headaches such as migraine and cluster headache.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4459752/

Main component of epigenetic coding



http://journal.frontiersin.org/article/10.3389/fncel.2015.00088/full

epigenetic targets corresponding with chronic pain.

Epigenetic target	Epigenetic effect	Region	Results
MicroRNAs	↑ miR-21	DRG	Mechanical allodynia and thermal hyperalgesia
	↓ miR-134	DRG	Up-regulation of μ-opioid receptor
	↓ miR-7a, ↓ miR-96	DRG	Nerve injury induced increases in voltage gated sodium channels
	↓ miR-124a	Spinal cord	Regulation pro-inflammatory marker genes
	↓ miR-200b, ↓ miR-249	NAc	Dysfunction of mesolimbic motivation circuitry
	↑ miR-155, ↑ miR-223	PFC	miRNA changes in the PFC, after inflammatory pain induced by facial carrageenan injection
DNA methylation	↓ Global DNA Methylation	PFC, AMY	Correlation with the magnitude of nerve injury-induced nociceptive sensitization
	↑ phosphorylation of MeCP2	Spinal cord	Correlation with magnitude of inflammation induced nociceptive sensitization
Histone modification	↓ HistoneH3K27me3	Spinal cord	Chemokine activation
	↑ HDAC1	Spinal cord	Hyperalgesia and allodynia in SNL were accompanied by HDAC1 overexpression
	↑ HDAC1, 2, & 4	NRM	Inflammatory and nerve injury associated suppression of *Gad2* transcription and disrupted GABA synaptic inhibition
	↑ HDAC2	Spinal cord	Thermal hyperalgesia

DRG: dorsal root ganglion; NAc: nucleus accumbens; PFC: prefrontal cortex; AMY: amygdala; NRM: nucleus raphe magnus.

- Epigenetic mechanisms modulate long-term changes in gene expression.
- Epigenetic activity correlates with behavioral manifestations of chronic pain.
- Targeting epigenetic pathways alters behavioral and molecular markers of pain.
- Focus on epigenetics may help reveal novel therapeutic targets for chronic pain.

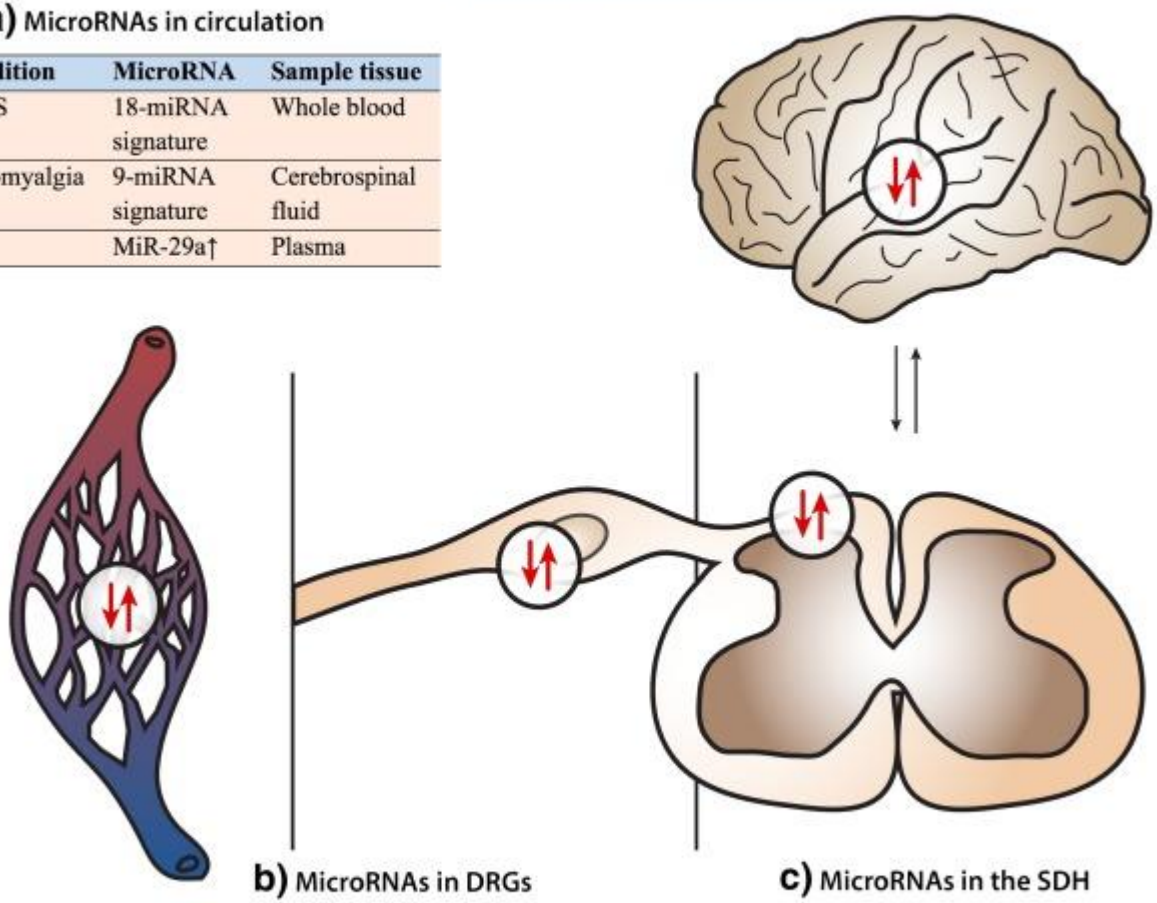
Trends Neurosci. 2015 Apr; 38(4): 237–246.

d) MicroRNAs in the brain

Condition	MicroRNA	Gene target
Inflammatory pain	MiR-200b, MiR-429↓	DNMT3a
Neuropathic pain	MiR-155↓	C/EBP*

a) MicroRNAs in circulation

Condition	MicroRNA	Sample tissue
CRPS	18-miRNA signature	Whole blood
Fibromyalgia	9-miRNA signature	Cerebrospinal fluid
IBS	MiR-29a↑	Plasma



b) MicroRNAs in DRGs

Condition	MicroRNA	Gene target
Inflammatory pain	MiR-134↑	MOR1
Neuropathic pain	MiR-183↓	CACNA1D*

c) MicroRNAs in the SDH

Condition	MicroRNA	Gene target
Inflammatory pain	MiR-181a↑	GABRA1
	MiR-124↓	MECP2
Neuropathic pain	MiR-29a↓	CACNA1C
	MiR-23b↓	NOX4

http://www.sciencedirect.com/science/article/pii/S0969996114002320

Mol Neurobiol (2016) 53:1494–1500
DOI 10.1007/s12035-015-9106-5

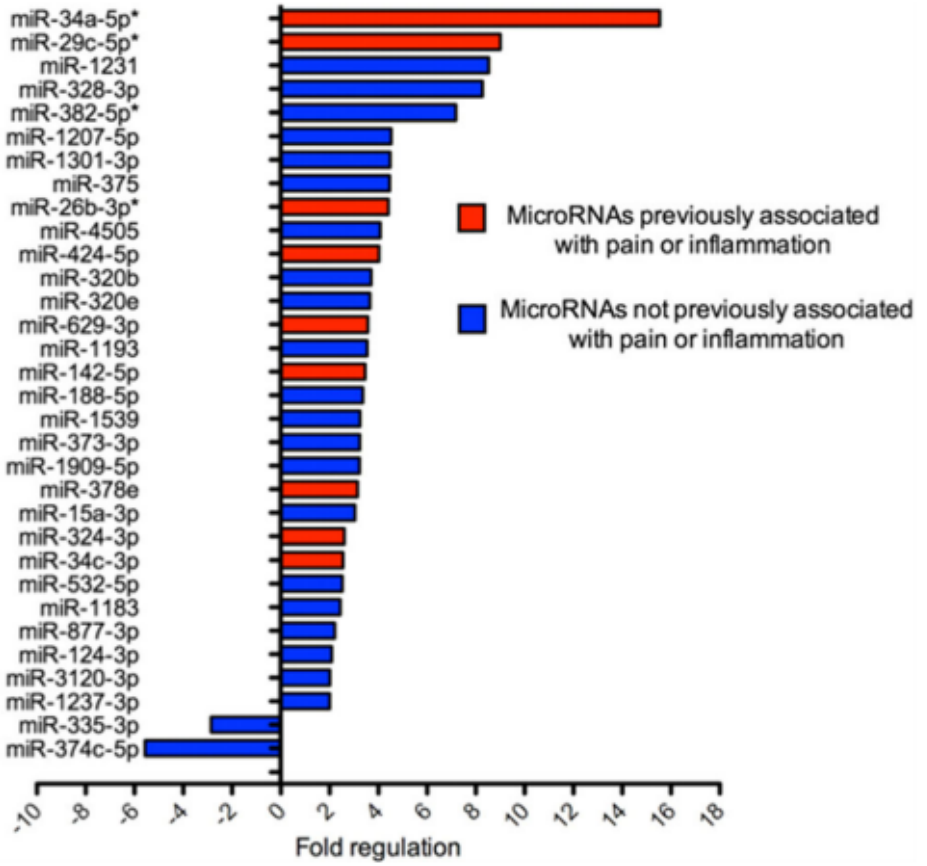
Serum MicroRNA Signatures in Migraineurs During Attacks and in Pain-Free Periods

Hjalte H. Andersen · Meg Duroux · Parisa Gazerani

Table 3 Predicted and validated target genes of each selected miRNA

MicroRNA	Gene abbreviation	Gene name
MiR-34a-5p	GABBR2	Gamma-aminobutyric acid type B receptor subunit 2
	SLC6A1[a]	Sodium- and chloride-dependent GABA transporter 1
	GABRA3	Gamma-aminobutyric acid receptor subunit alpha-3
MiR-29c-5p	IL4[a]	Interleukin 4
	IL1RA[a]	Interleukin-1 receptor antagonist
MiR-382-5p	IL10RA	Interleukin 10 receptor, alpha subunit
	GABRA5	Gamma-aminobutyric acid receptor subunit alpha-5
MiR-26b-3p	GABRG1	Gamma-aminobutyric acid receptor subunit gamma-1
	GABRA4	Gamma-aminobutyric acid receptor subunit alpha-4

[a] Previously experimentally validated gene targets



http://link.springer.com/article/10.1007%2Fs12035-015-9106-5

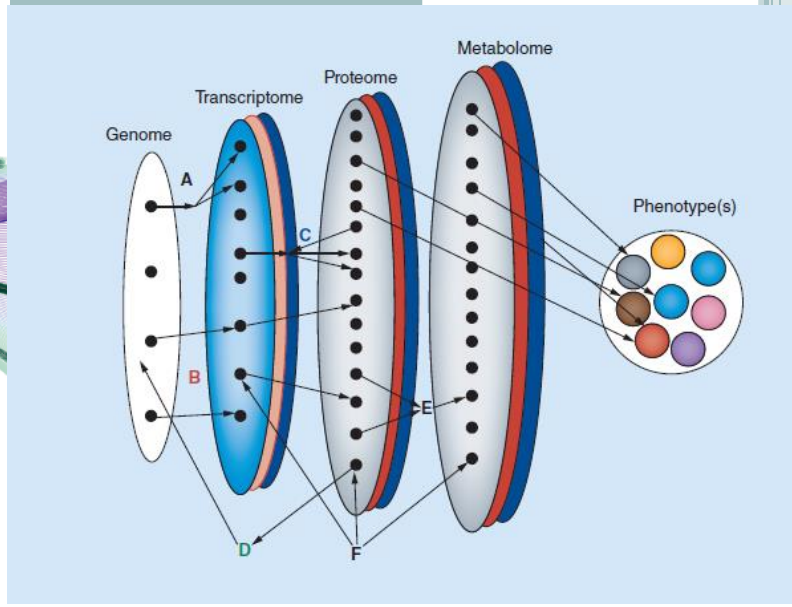
Future NEUROLOGY

REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

'Omics': an emerging field in pain research and management

Parisa Gazerani*[1] & Hye Sook Han Vinterhøj[1]



A general model of omics in complex disease. Variation in the genome is represented in the transcriptome which is presented in the proteome. Each level is represented by an oval. For the genome each dot in the oval is a different gene or sequence variant. These variants are expressed as part of the transcriptome. However, unlike the genome which is essentially invariant among cells and tissues the transcriptome can differ substantially. Different tissues are represented by overlapping ovals. Similarly, the transcriptome is translated into the proteome differently in different tissues (again represented as overlapping ovals). The proteome affects the metabolome in a tissue specific manner and the latter two ultimately influence the phenotype.

This simple model is modified by multiple factors within and among levels noted on the figure as: (A) Differential splicing that can be affected by the proteome; (B) siRNA and/or miRNA; (C) post-translation modification of proteins; (D) transcription factor binding; (E) receptor–ligand binding; (F) environmentally induced factors such as epigenetic modifications, mutagenesis or modifier of gene expression.

Future NEUROLOGY

EDITORIAL

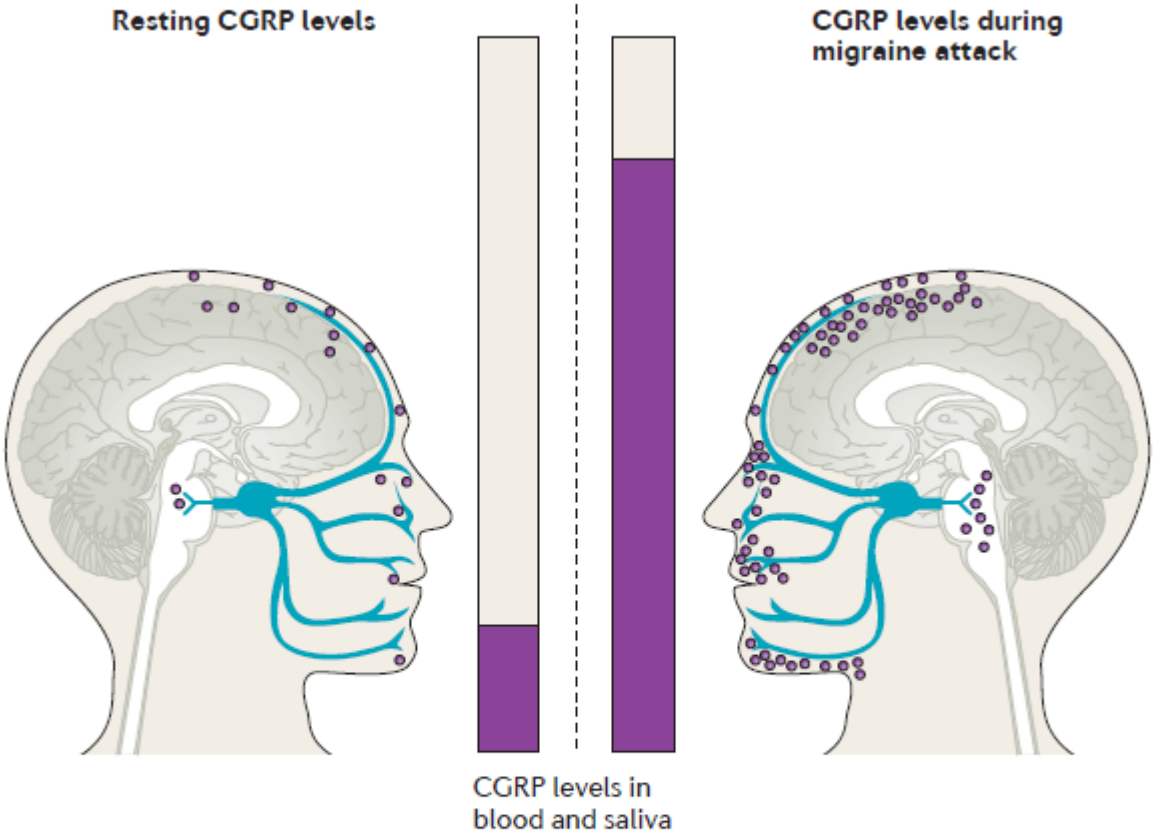
Toward mechanism-based treatment of migraine: spotlight on CGRP

Parisa Gazerani*

"...development of mAbs (and CGRP-RAs) highlights the value and importance of translational research, where CGRP linked to migraine pathogenesis guided the development of target-specific compounds..."

Selective agents

- Calcitonin gene-related peptide (CGRP) is the best-validated therapeutic target for migraine
- Monoclonal antibodies (mAbs) against CGRP or its receptor hold promise for migraine prevention, and small-molecule CGRP antagonists hold promise for acute and/or preventive treatment



CGRP levels during migraine attacks. Calcitonin gene-related peptide (CGRP) is released from trigeminal sensory afferents and the spinal trigeminal nucleus. During migraine attacks, CGRP levels in the blood and saliva are increased. Administration of exogenous CGRP can induce migraine. Several therapeutics that target the CGRP pathway to treat primary headache disorders are in development.

| Phase III randomized controlled trials of monoclonal antibodies against CGRP or its receptor

Study	Primary efficacy outcomes	Administration route, frequency and duration	Study groups	Sample	Estimated primary completion	Location
LY2951742						
EVOLVE-1 (REF. 36)	Reduction of MD/M	SC, every month for 6 months	Two doses and placebo	825 patients with episodic migraine	February 2017	USA
EVOLVE-2 (REF. 37)	Reduction of MD/M	SC, every month for 3 months	Two doses and placebo	825 patients with episodic migraine	June 2017	USA
REGAIN[38]	Reduction of MD/M	SC, every month weeks for 2 months	Two doses and placebo	825 patients with chronic migraine	February 2017	USA
Episodic cluster headache study[39]	Reduction of weekly cluster attacks	SC, every month for 6 months	One dose and placebo	162 patients with episodic cluster headache	December 2016	North America and Europe
Chronic cluster headache study[40]	Reduction of weekly cluster attacks	SC, every month weeks for 3 months	One dose and placebo	162 patients with chronic cluster headache	November 2016	USA and Europe
ALD403						
PROMISE 1 (REF. 44)	Difference in responder rate	IV, one dose with primary outcome at 12 weeks	Three doses and placebo	600 patients with episodic migraine	January 2017	USA
PROMISE 2 (Episodic migraine)	Not announced	Not announced	Not announced	Not announced	Not announced	Not announced
TEV-48125						
Episodic migraine study[45]	Reduction of MD/M	SC, every 28 days for 12 weeks	Two doses and placebo	786 patients with episodic migraine	September 2017	USA and Israel
Chronic migraine study[46]	Reduction of HD/M	SC, every 28 days for 12 weeks	Two doses and placebo	1020 patient with chronic migraine	September 2017	North America, Europe and Israel
AMG 334						
STRIVE[49]	Reduction of MD/M	SC, every month for 6 months	Two doses and placebo	852 patients with episodic migraine	August 2016	North America and Europe
ARISE[50]	Reduction of MD/M	SC, every month for 3 months	One dose and placebo	540 patients with episodic migraine	July 2016	USA and Europe
Chronic migraine study[51]	Reduction of MD/M	SC, every month for 3 months	Two doses and placebo	667 patients with chronic migraine	February 2016	North America and Europe

CGRP, calcitonin gene-related protein; HD/M, headache days per month; IV, intravenous; MD/M, migraine days per month; SC, subcutaneous.

Glial Cells: New Targets for Chronic Pain

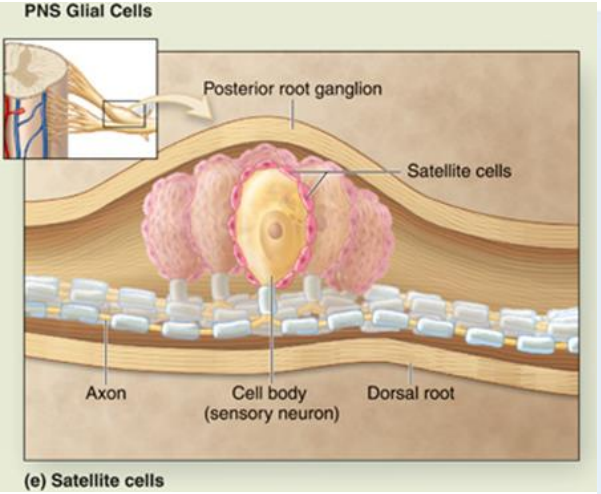
One of the newest approaches to the treatment of pathological pain by the control of glial activation

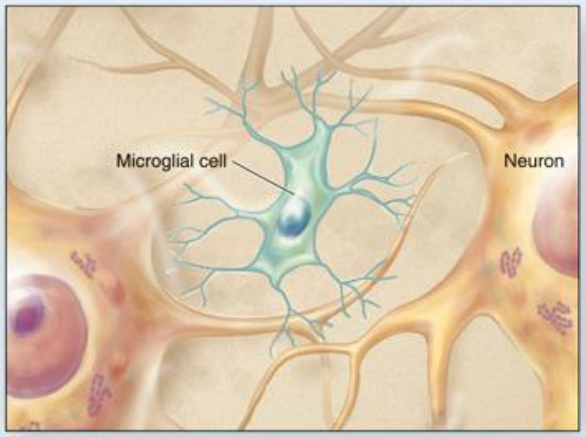
Distinct reaction of microglia, astrocytes, and satellite glial cells (SGCs) in different pain conditions, as examined by upregulation of the glial markers IBA1, CD11b, and glial fibrillary acidic protein (GFAP).

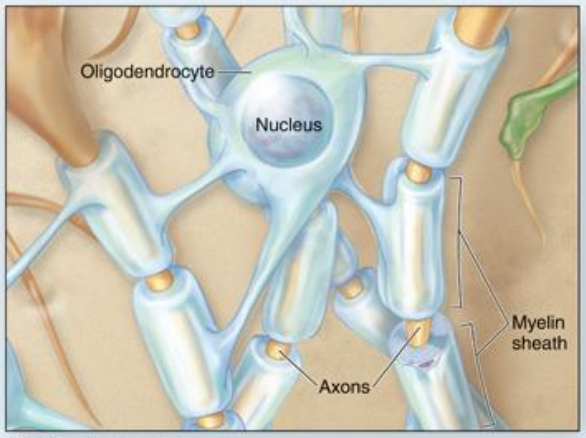
Pain conditions	Microglia	Astrocytes	SGCs
Nerve injury	↗	↗	↗
Spinal cord injury	↗	↗	
Paw incision	↗	↗	
Inflammation	↔/↗	↗	↗
Joint arthritis	↗	↗	↗
Bone cancer	↔/↗	↗	↗
Skin cancer	↔	↗	
Chemotherapy	↔/↗	↗	↗
Diabetes	↗	↗	
HIV neuropathy	↔	↗	
Chronic opioid	↗	↗	
Acute opioid	↔	↔	↗

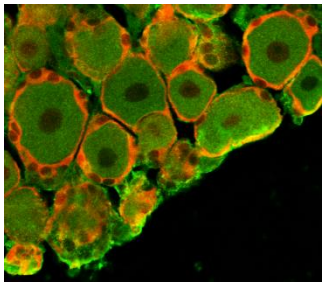
Detailed, with related references, in Section 2.1.
Symbols: Right-upward diagonal arrow (↗) denotes upregulation; right&left horizontal arrow (↔) denotes no regulation; right-downward diagonal arrow (↘) denotes downregulation.

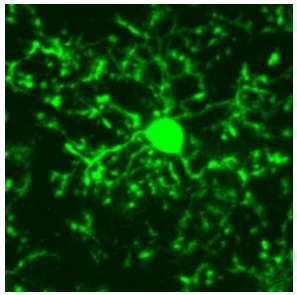
Nature Reviews Drug Discovery 2, 973-985 (December 2003)
PAIN 154 (2013) S10–S28

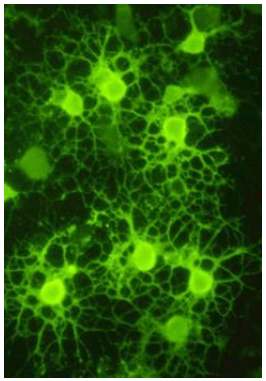


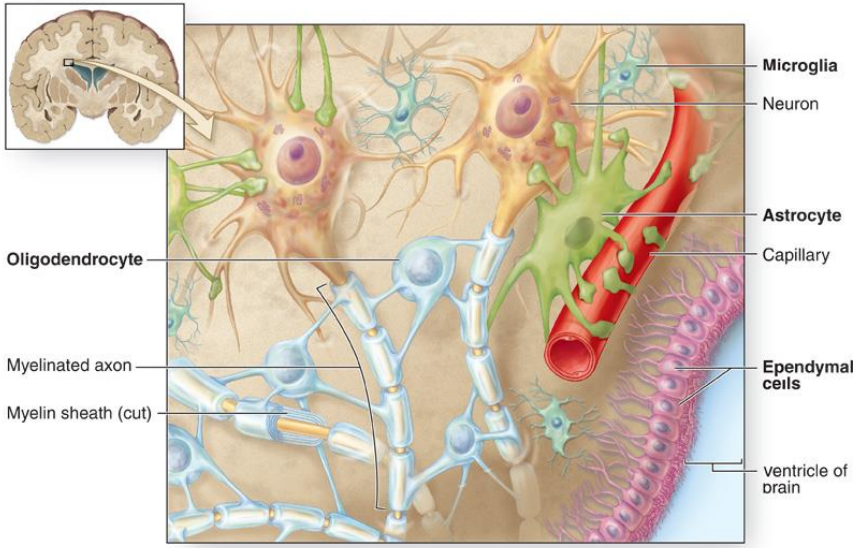


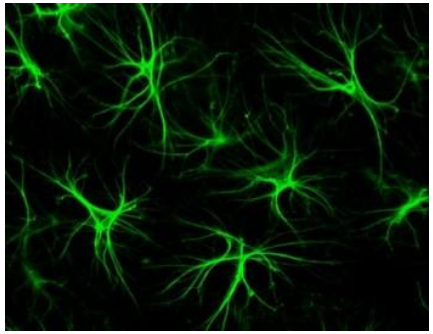












1. Glial reaction: changes of glial markers and morphology

2. Regulation of receptors, channels, and transporters in glia

↑↓

3. Phosphorylation of MAP kinase signaling pathways in glia

↓

4. Production of cytokines, chemokines, growth factors in glia

↓

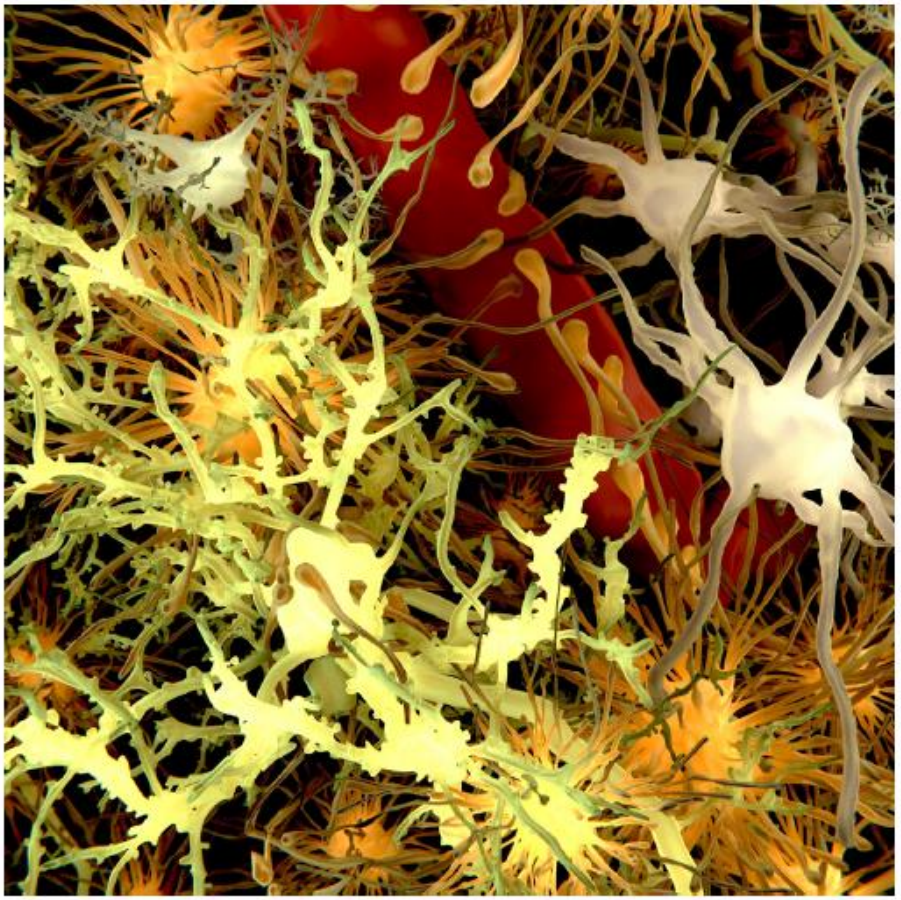
Release of glial mediators

↓

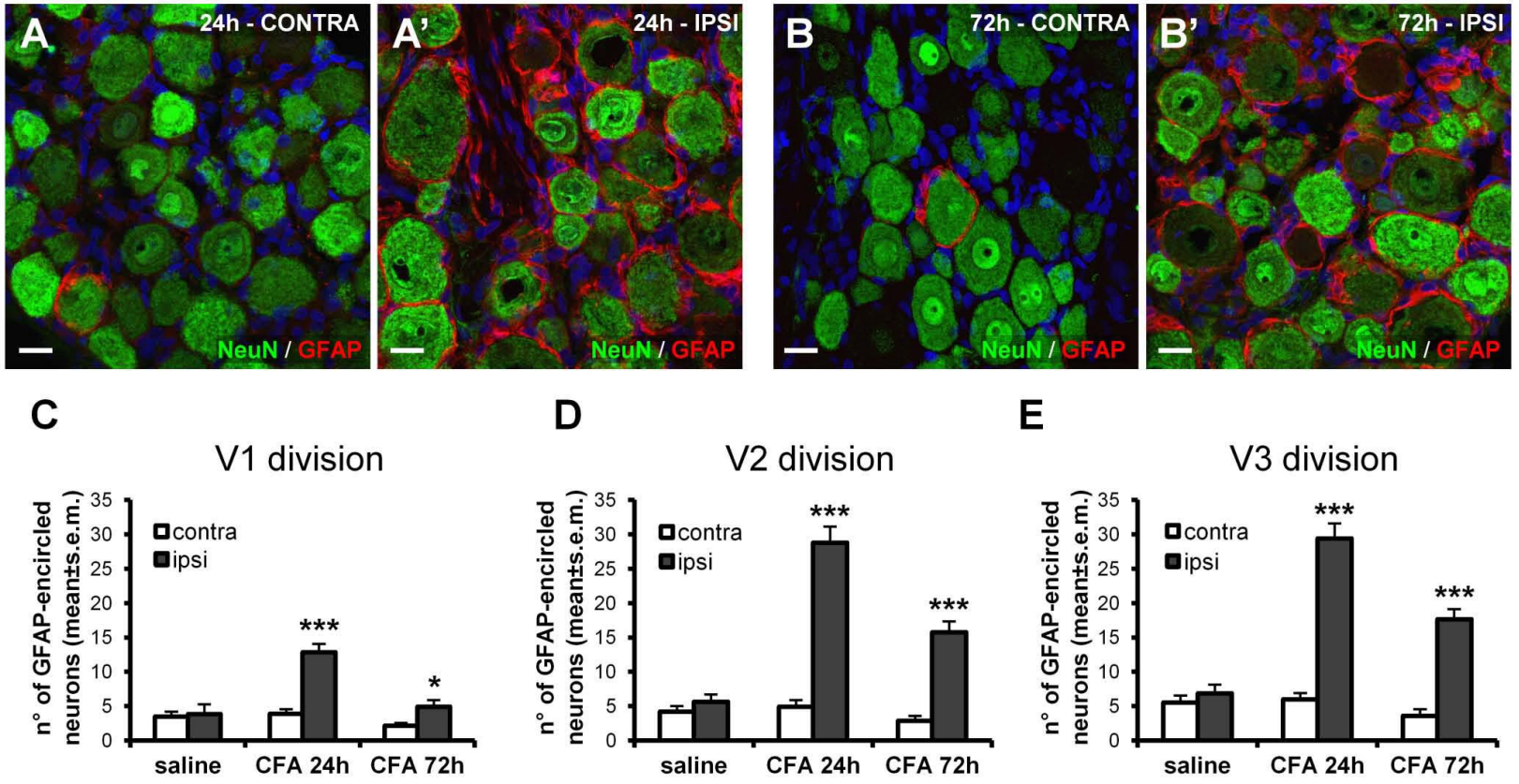
Interaction with neurons: central and peripheral sensitization

↓

Persistent pain



It is complicated. The main cells of the brain: astrocytes-orange; neurons-light yellow/greenish; oligodendrocytes-grey; and microglia-white. Also pictured is a blood vessel-red. Picture used with permission from Shutterstock.com, Juan Gartner.



GFAP immunoreactivity is increased in SGCs following induction of TMJ inflammation

Future NEUROLOGY

EDITORIAL

Targeting glia in human pain: challenges and opportunities

"*In vivo* glial imaging seems a reliable method to assist in understanding gliopathy in human pain..."

Parisa Gazerani*

First draft submitted: 25 April 2016; Accepted for publication: 11 May 2016; Published online: 13 July 2016

Open Access Full Text Article

ORIGINAL RESEARCH

A double-blind, randomized, placebo-controlled pilot trial to determine the efficacy and safety of ibudilast, a potential glial attenuator, in chronic migraine

This article was published in the following Dove Press journal:
Journal of Pain Research
31 October 2016
Number of times this article has been viewed

Yuen H Kwok[1]
James E Swift[1]
Parisa Gazerani[2]
Paul Rolan[1]

[1]Discipline of Pharmacology, University of Adelaide, Level 5 Medical School North, South Australia, Australia; [2]Department of Health Science & Technology, Aalborg University, Aalborg, Denmark

Background: Chronic migraine (CM) is problematic, and there are few effective treatments. Recently, it has been hypothesized that glial activation may be a contributor to migraine; therefore, this study investigated whether the potential glial inhibitor, ibudilast, could attenuate CM.

Methods: The study was of double-blind, randomized, placebo-controlled, two-period crossover design. Participants were randomized to receive either ibudilast (40 mg twice daily) or placebo treatment for 8 weeks. Subsequently, the participants underwent a 4-week washout period followed by a second 8-week treatment block with the alternative treatment. CM participants completed a headache diary 4 weeks before randomization throughout both treatment periods and 4 weeks after treatment. Questionnaires assessing quality of life and cutaneous allodynia were collected on eight occasions throughout the study.

Results: A total of 33 participants were randomized, and 14 participants completed the study. Ibudilast was generally well tolerated with mild, transient adverse events, principally nausea. Eight weeks of ibudilast treatment did not reduce the frequency of moderate to severe headache or of secondary outcome measures such as headache index, intake of symptomatic medications, quality of life or change in cutaneous allodynia.

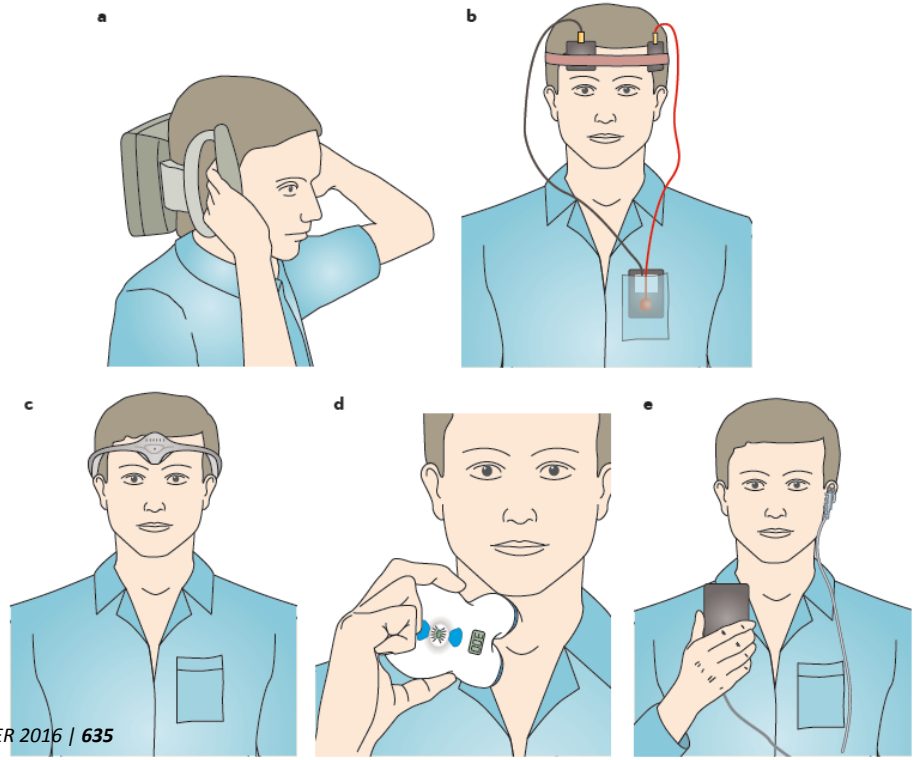
Conclusion: Using the current regimen, ibudilast does not improve migraine with CM participants.

Keywords: chronic migraine, glia, ibudilast, headache, immune system

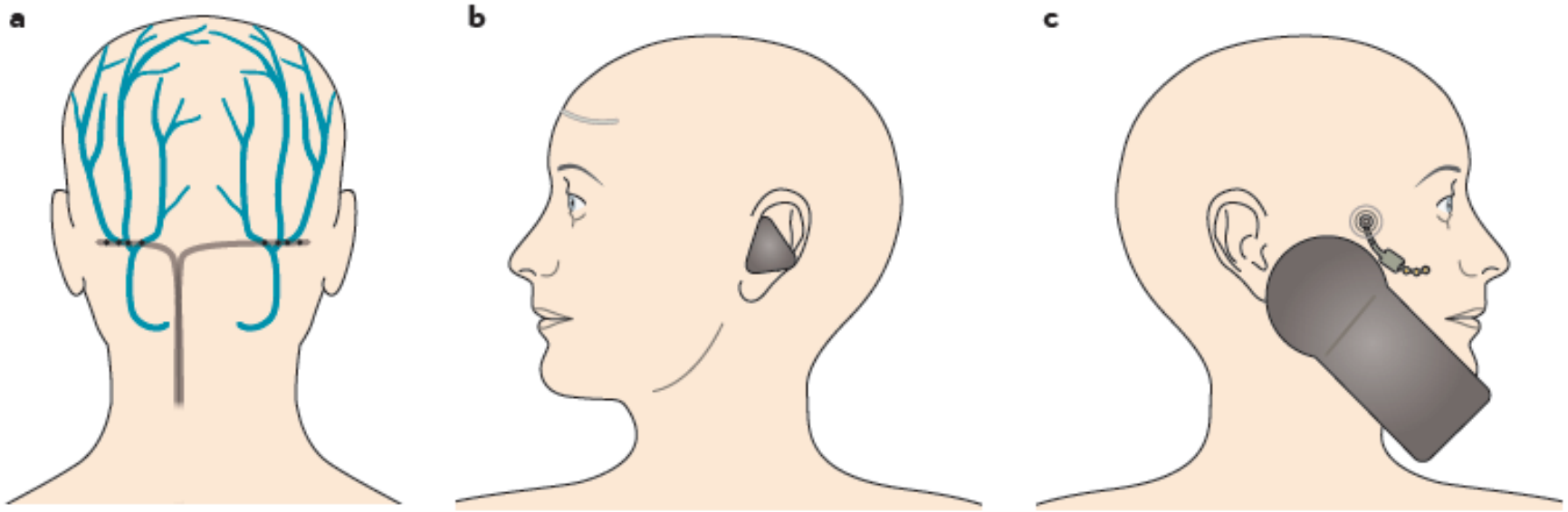

TIME FOR A BREAK

Non-invasive neuromodulation treatments

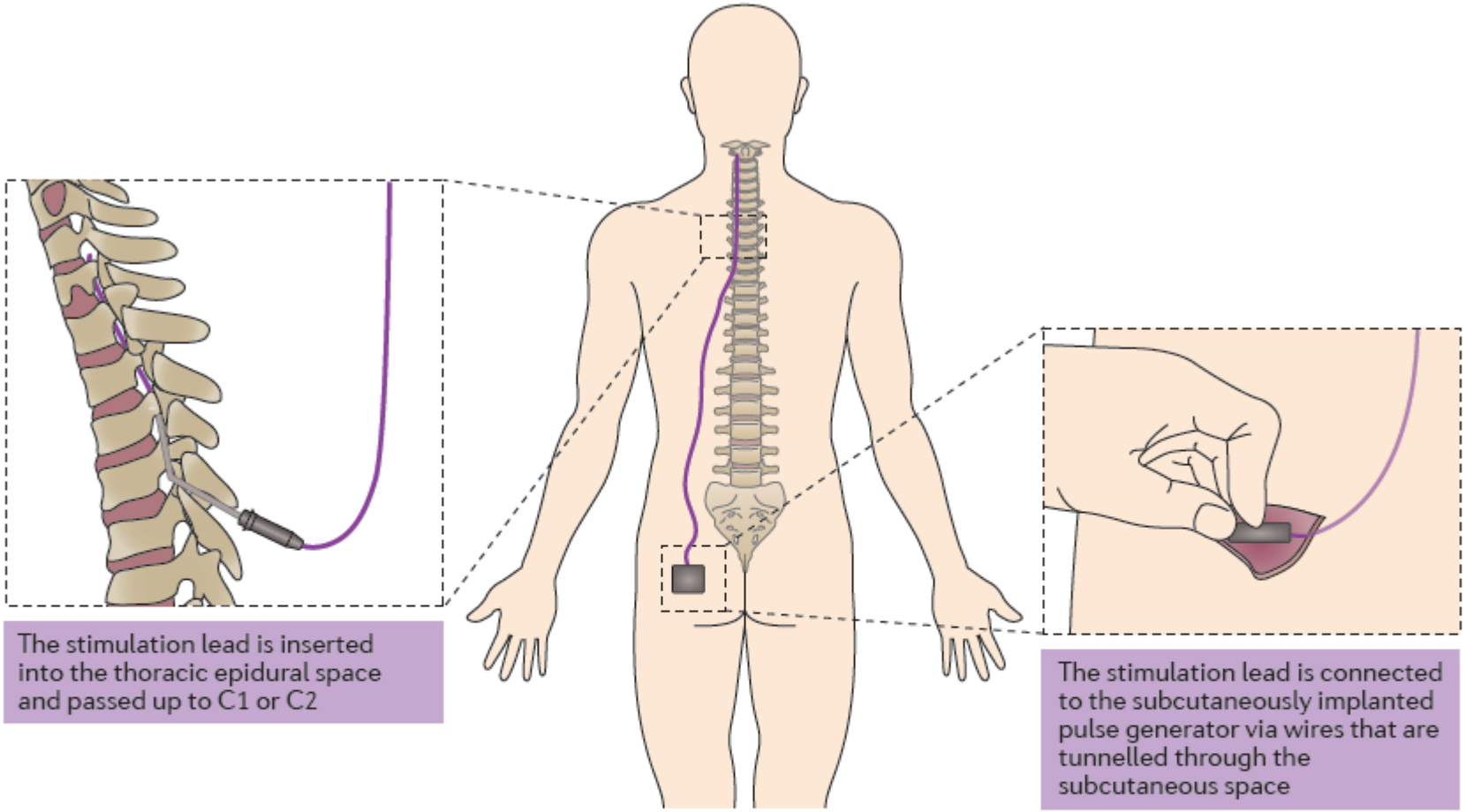
a) SpringTMS (eNeura Inc., Sunnyvale, California, USA) is a portable transcranial magnetic stimulation device that is used to treat migraine with aura. B) Transcranial direct current stimulation devices are noninvasive, portable treatments that deliver an electrical current via a cathode and an anode that are strapped to the patient's head. c) The Cefaly device (Cefaly Technology, Grâce-Hollogne, Belgium) is a noninvasive pericranial peripheral nerve stimulator that is placed over the forehead. The smaller Cefaly II is now available in the USA. d) The gammaCore device (electroCore LLC, Basking Ridge, New Jersey, USA) is a handheld noninvasive vagal nerve stimulator. e) The NEMOS device (Cerbomed, Erlanger, Germany) is a portable transcutaneous stimulator that targets the auricular branch of the vagus nerve. An ear electrode is worn in contact with the skin of the concha, similar to a hearing aid, and the device is powered by a handheld, battery powered electrical stimulator.



TENS:
Either block painful signaling or provoke release of endogenous opioids

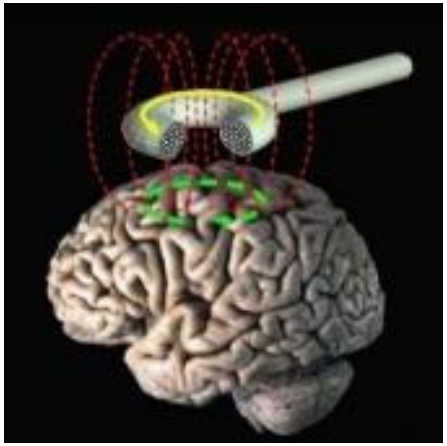


Implantable neuromodulation treatments. a | Implantable occipital nerve stimulators are a type of peripheral nerve stimulator. The electrodes are implanted over the occipital nerves. **b** | The StimRelieve Halo Migraine System (Stimwave LLC, Fort Lauderdale, Florida, USA) is a wirelessly controlled peripheral nerve stimulator. The device uses percutaneously placed leads which are powered by a wireless external unit via radiofrequency signals rather than by an implantable pulse generator. Use of wireless technology to power the device removes the need for surgical tunnelling and creation of a pocket for battery implantation, and reduces the risk of lead migration because the leads are not attached to an implanted battery that can cause pulling. The stimulation leads can be placed over multiple pericranial peripheral nerves. **c** | The Pulsante SPG neurostimulator system (Autonomic Technologies, Inc., Redwood City, California, USA) is a multichannel peripheral nerve stimulator that is implanted transorally into the pterygopalatine fossa. It is controlled by a handheld remote control that is placed over the cheek to apply therapy. SPG, sphenopalatine ganglion.

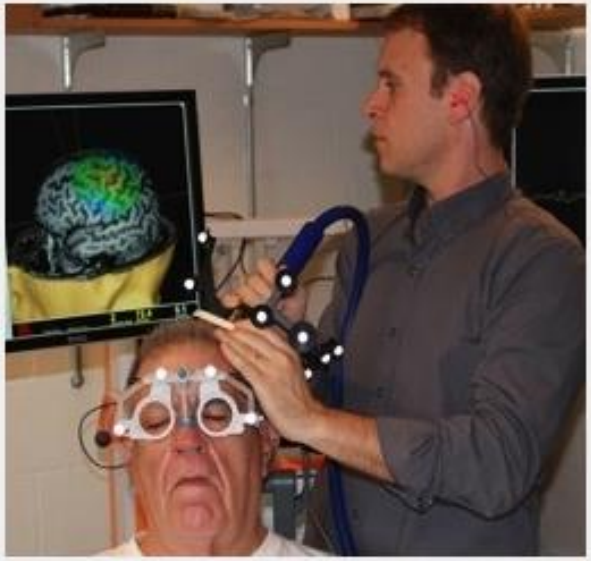


High cervical spinal cord stimulators. High cervical spinal cord stimulation is performed by introducing a needle into the upper thoracic epidural space and advancing a wire lead through the needle superiorly until the distal tip reaches — depending on the clinical study — the C1 or C2 level. Typically, a trial implantation, during which the stimulator leads are placed and connected to an external battery, is performed first. The trial implantation is an outpatient procedure that can be performed in under an hour. If the stimulator is tolerated and effective, permanent implantation, during which the wires are tunnelled to a subcutaneous pocket where the battery is implanted, is performed at a later date.

Transcranial Magnetic Stimulation: The Next Wave in Pain Treatment?



In TMS, a magnetic field generated outside the head alters circuit activity inside the brain. TMS was approved in 2008 by the U.S. Food and Drug Administration for treatment of major depression, and researchers are investigating TMS for a number of other neurological conditions, including chronic, intractable pain…



In MRI-guided TMS, the operator holds the figure-eight coil to the patient's scalp while monitoring the brain stimulation site on the three-dimensional MRI. Stereotactic spheres mounted on the coil identify its position relative to the spheres on the goggles that localize the patient's head. Credit: Roi Treister, Massachusetts General Hospital, Boston, US

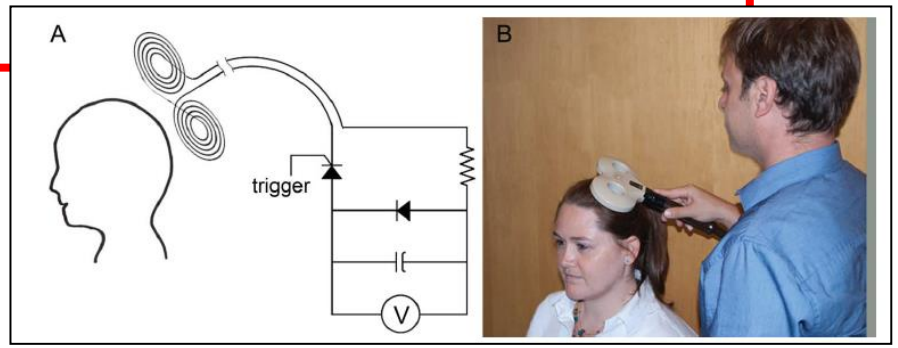
Comprehensive Review

PAIN®

Transcranial magnetic stimulation of the brain: guidelines for pain treatment research

Max M. Klein[a,*], Roi Treister[a], Tommi Raij[b], Alvaro Pascual-Leone[c], Lawrence Park[d,e], Turo Nurmikko[f], Fred Lenz[g], Jean-Pascal Lefaucheur[h,i], Magdalena Lang[a], Mark Hallett[j], Michael Fox[a,b,c], Merit Cudkowicz[a], Ann Costello[d], Daniel B. Carr[k], Samar S. Ayache[h,i], Anne Louise Oaklander[a,l]

- In transcranial magnetic stimulation (TMS), electromagnetic coils held against the scalp influence underlying cortical firing. Multiday repetitive transcranial magnetic stimulation (rTMS) can induce long-lasting, potentially therapeutic brain plasticity.
- Adverse effects are minimal, primarily headaches.
- Single provoked seizures are very rare.

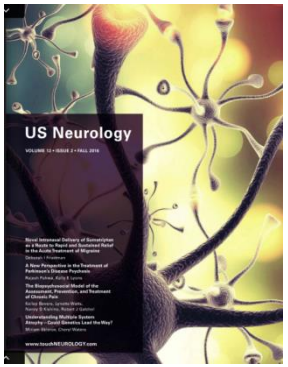


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4545735/

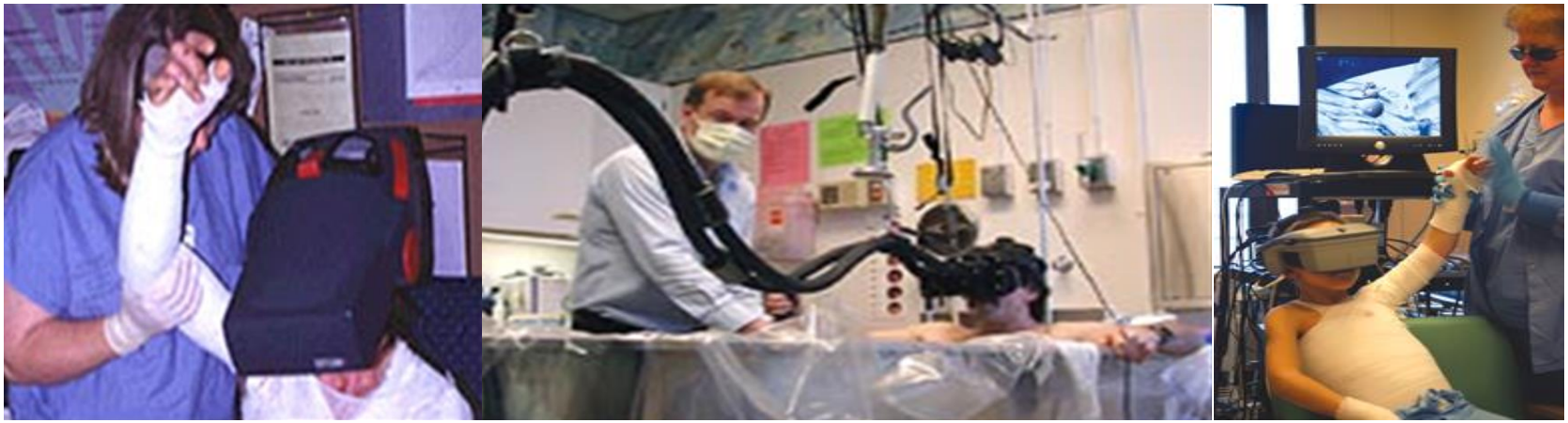
Virtual Reality for Pain Control – Virtual or Real?

Parisa Gazerani

Department of Health Science and Technology, Aalborg University, Denmark



Virtual Reality (VR) technology creates a sense of immersion in a virtual environment analogous to the real world. VR has increasingly gained attention for pain management based on current evidence demonstrating its analgesic effects in certain experimental, acute and chronic pain conditions. VR-based interventions shift the users' attention towards active cognitive processing that can lead to higher pain threshold or tolerance. An understanding of neurobiological mechanisms underlying analgesic effects of VR will definitely facilitate optimal utility of this tool for pain control.



http://www.touchneurology.com/journals/editions/us-neurology-volume-12-issue-2-fall-2016

A simulation used in pain remediation. Specifically, it has been applied to burn victims for distraction to reduce the pain of bandage changing. A user navigates the environment, which is designed to conjure thoughts of cold, during treatment. The distraction created with this simulation has yielded impressive pain reduction results, over and above the pain reduction produced by opioid pain medications.

https://www.youtube.com/watch?v=jNIqyyypojg

Future directions

- There is a clear need for studies to help develop and refine VR protocols for managing persistent pain.
- The efficacy of VR in different populations of persons having persistent pain needs to be determined.
- The efficacy of VR for persistent pain may vary across age groups.
- New software technologies are needed to support the creation of custom environments. New 3-D modeling and VR design software may be developed with the goal of making designing custom VR therapies.
- One important research issue is how to enhance generalization of treatment effects from a VR environment to daily situations in which pain is a problem.
- In VR, one can directly expose patients to progressively more difficult pain-related situations inside the clinic in order to foster more adaptive coping responses to pain.
- Research on VR interventions for persistent pain is in its infancy. This technology, however, holds considerable promise.

EXPERT REVIEWS

Venom-based biotoxins as potential analgesics

Expert Rev. Neurother. Early online, 1–14 (2014)

Parisa Gazerani*[1,2] and
Brian Edwin Cairns[1,3]

Table 1. Main μ- and μO-conotoxins targeting sodium channels (Na_V).

Conotoxins	*Conus* species	Na_V subtype
μ-conotoxins		
KIIIA	*C. kinoshitai*	$Na_V1.3$, $Na_V1.7$
SIIIA/B (PEG-SIIIA)	*C. striatus*	$Na_V1.3$, $Na_V1.7$, $Na_V1.8$
PIIIA	*C. purpurascens*	$Na_V1.3$, $Na_V1.7$
PnIVA/B	*C. pennaceus*	Molluscan
GIIIA/B/C	*C. geographus*	$Na_V1.4$, *not completely determined*
CnIIIA/B/C	*C. consors*	$Na_V1.3$, $Na_V1.7$, $Na_V1.8$
CIIIA	*C. catus*	*Not determined*
SIIIA/B	*C. striatus*	$Na_V1.2$, $Na_V1.4$
SmIIIA	*C. stercusmuscarum*	$Na_V1.3$, $Na_V1.7$
MIIIA	*C. magus*	Nav1.3, Nav1.7
SxIIIA/B	*C. striolatus*	*Not determined*
BuIIIA/B/C	*C. bullatus*	$Na_V1.3$
TIIIA	*C. tulipa*	$Na_V1.3$, $Na_V1.7$, $Na_V1.8$
μO-conotoxins		
MrVIA	*C. marmoreus*	$Na_V1.7$
MrVIB	*C. marmoreus*	$Na_V1.3$, $Na_V1.7$, $Na_V1.8$
MfVIA	*C. magnificus*	$Na_V1.3$, $Na_V1.7$, $Na_V1.8$
LtVIIA V, LtVd V, LtVIC V	*C. litteratus*	*Not determined*
Conotoxin-GS	*C. geographus*	$Na_V1.2$, $Na_V1.4$, *not completely determined*

Table 2. Currently known targets of venom-based peptidergic biotoxins presented in this review (cont.).

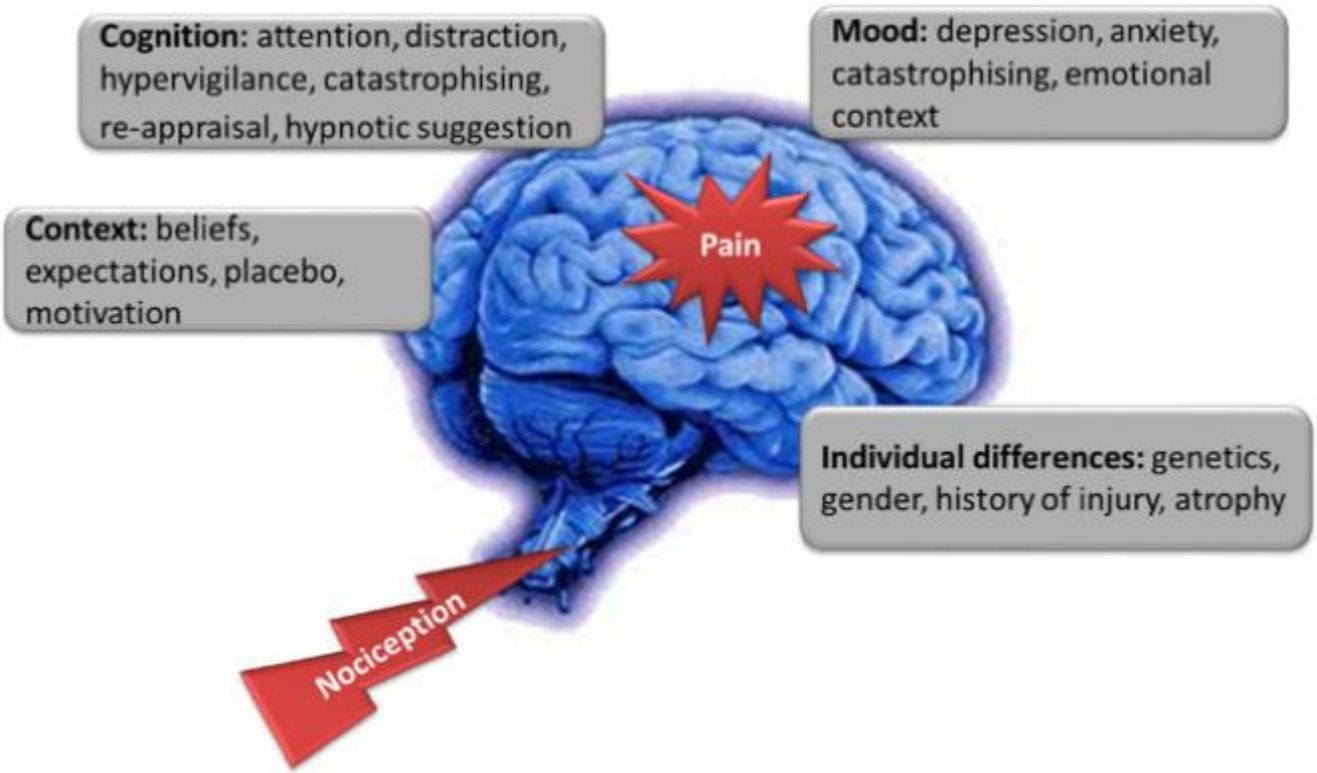
Target	Action	Venom	Venomous source
Acid-sensing ion channels	Inhibition	Mambalgins psalmotoxin-1 APETx-2	Black mamba snake: *Dendroaspis polylepis polylepis* South American tarantula: *Psalmopoeus cambridgei* Sea anemone: *Anthopleura elegantissima*
TRP channels	Inhibition	APHC1	Sea anemone: *Heteractis crispa*
hERG channels	Inhibition	GsMTx4	Chinese rose tarantula spider: *G. spatulata*
MAPK pathway	Inhibition	BmK AGAP	Chinese scorpion: *Buthus martensii Karsch*
Neurotensin receptors	Activation	Contulakin (Cont-G)	Conus snail: *Conus geographus*
B_2 bradykinin receptors	Activation	Thr6-BK	European scolid wasp: *Megascolia flavifrons* and Brazilian social wasp: *Polybia occidentalis*

AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; hERG: Human ether-a-go-go related gene; NMDA: *N*-methyl-D-aspartate; TRP: Transient receptor potential channels.

Several pharmaceutical companies have recently re-focused on biotoxins and some new companies have been established specially for this purpose. This has led to a large number of lead compounds in the pipeline for both preclinical and clinical tests. The development of therapeutic agents based on venom-derived peptides is not an exception. The focus is not only on the efficacy and safety of venom-derived peptides, but also to improve delivery.

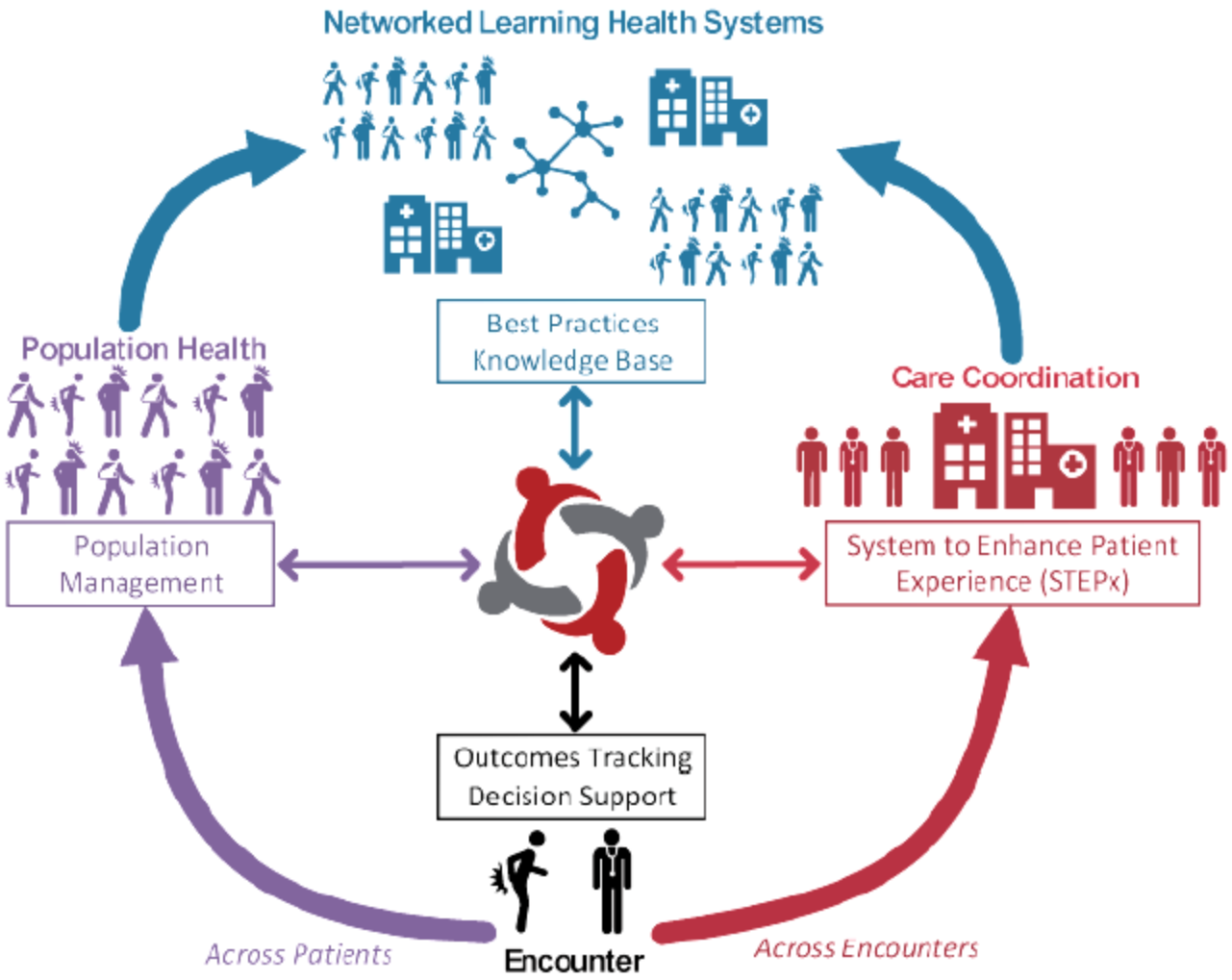
A large range of animal venoms can be purified and studied in detail because of novel advanced analytical techniques and high-throughput screening.

Multidimensional aspects of pain



Pain is an integrative sum of nociceptive input (i.e. signals from periphery during injury or surgery) combined with multiple factors that modulate this input to generate the complex and individual experience of pain.

Hand Clin. 2016 February ; 32(1): 91–98.



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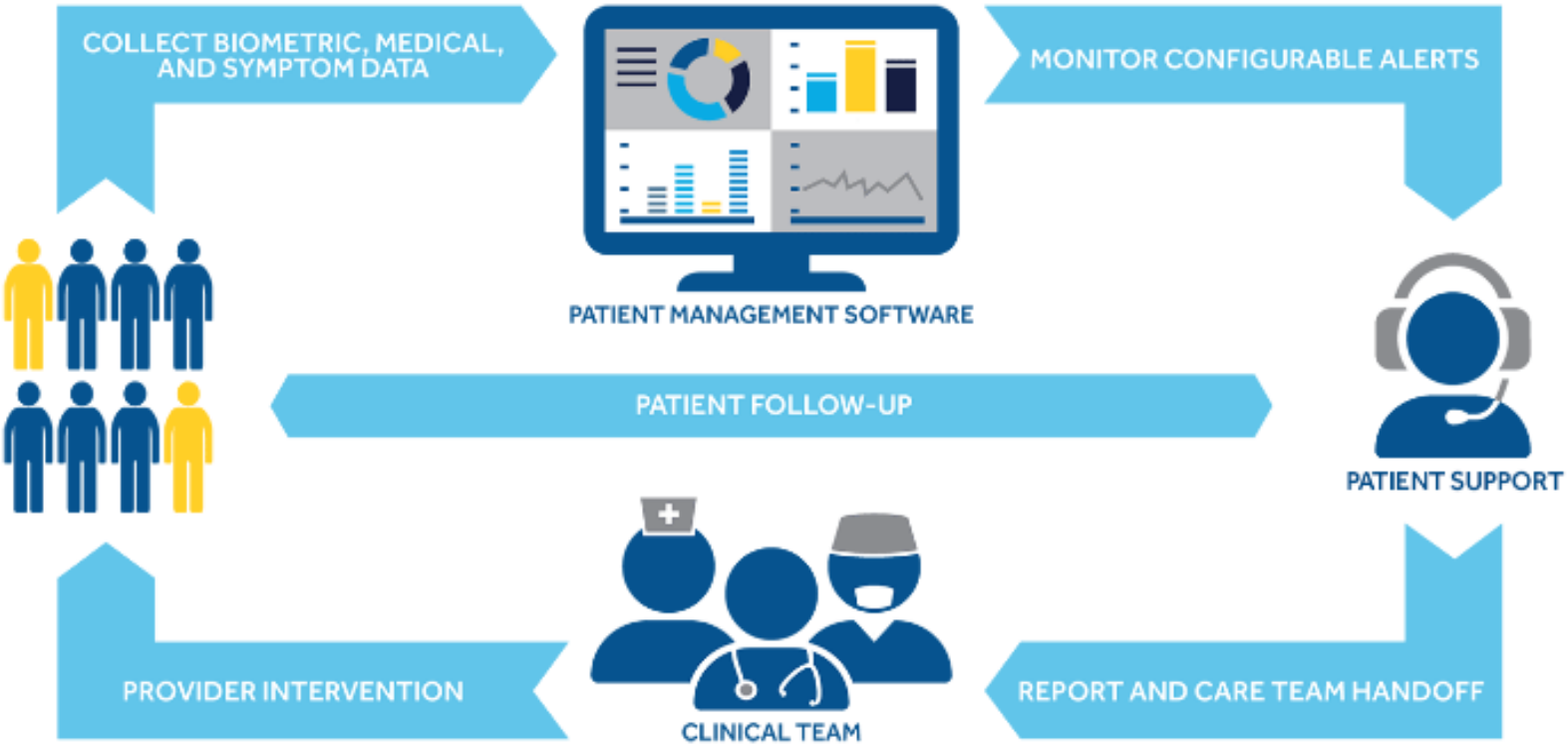
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