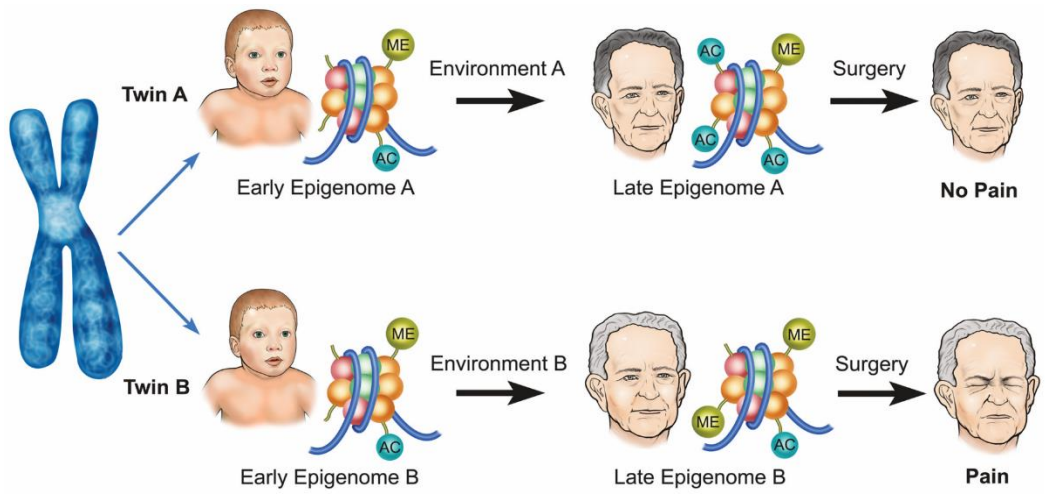
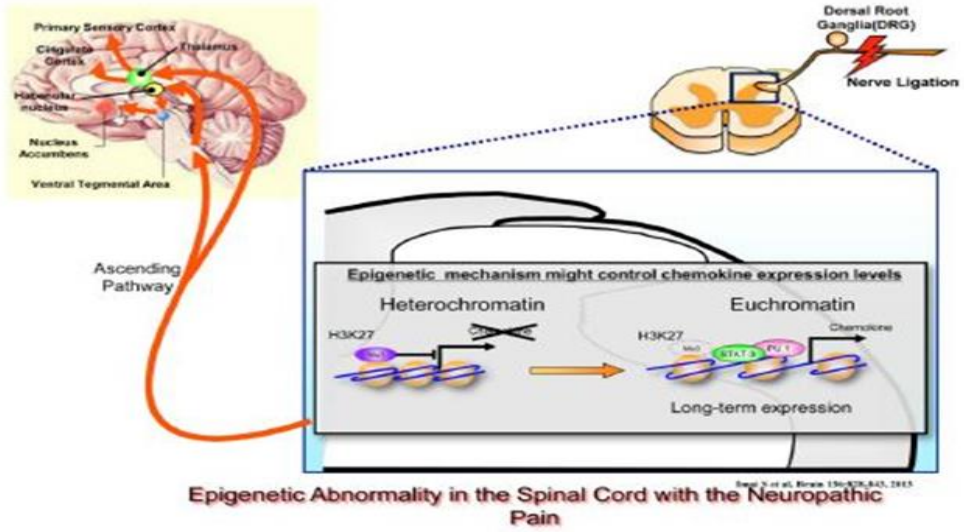
Epigenetic and Pain



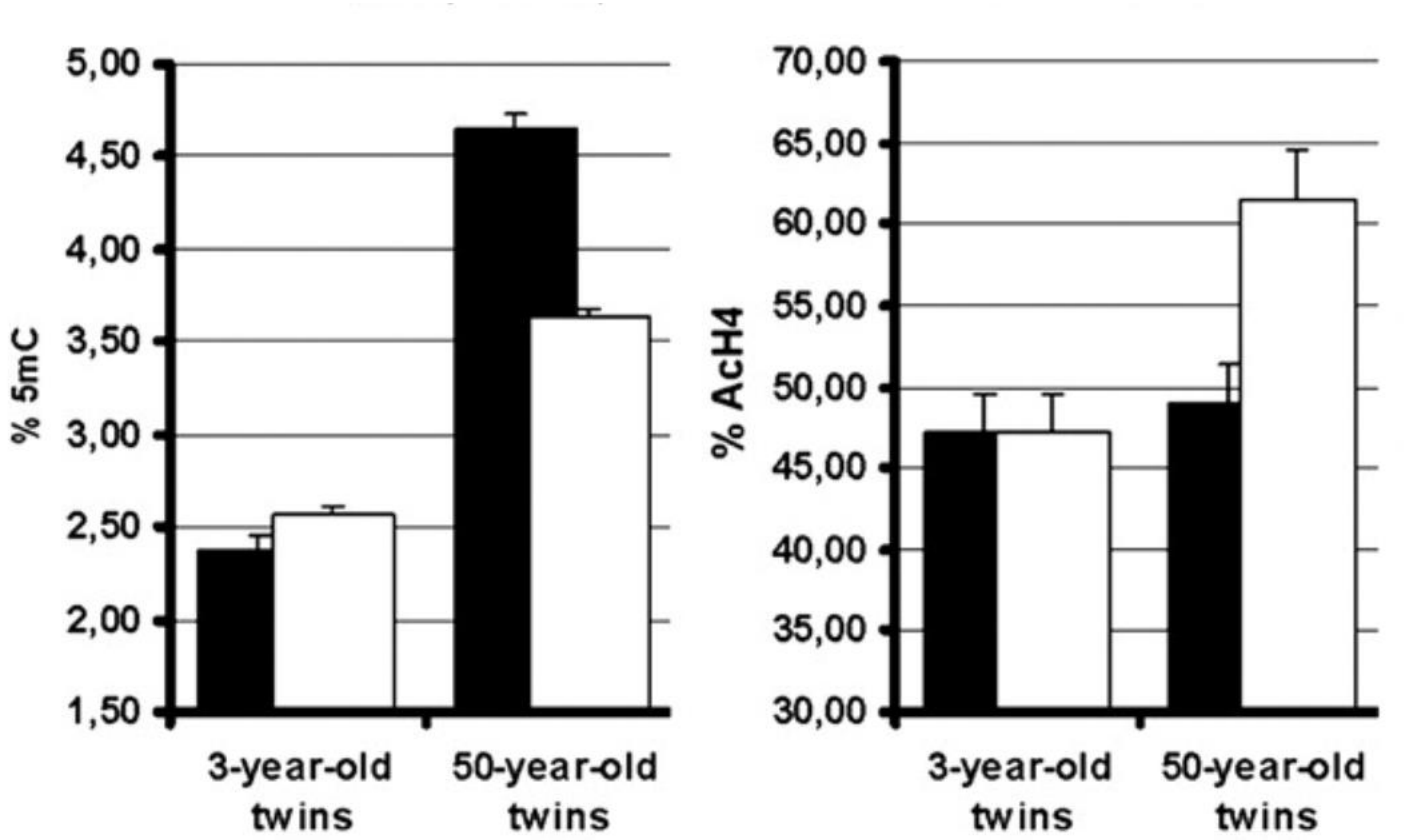


Epigenetic Abnormality in the Spinal Cord with the Neuropathic Pain

Figure 1. Epigenetic abnormality in the spinal cord during neuropathic pain
Long-term increases in chemokine expression may cause epigenetic modifications in the spinal cord, and thus may have a crucial role in chronic pain mechanisms. Nerve injury activates primary afferent nociceptors, which transmit information to the dorsal horn of the spinal cord. Activation of secondary neurons in spinal pathways by long-term chemokine expression can induce epigenetic modifications that may produce central sensitization leading to a neuropathic pain-like state. Reproduced from (30).

Proc Natl Acad Sci U S A. 2005 Jul 26;102(30):10604-9. Epub 2005 Jul 11.

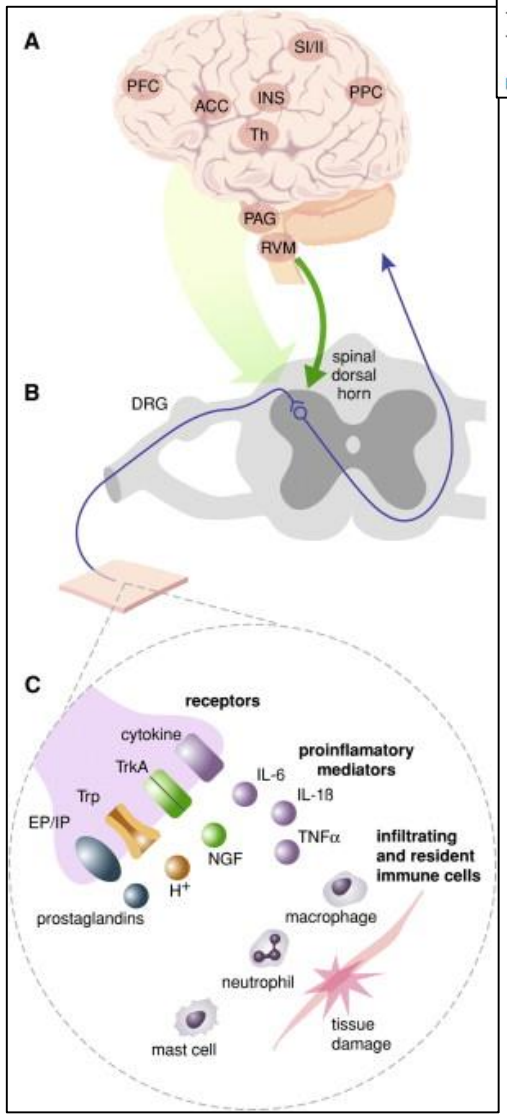
Epigenetic differences arise during the lifetime of monozygotic twins.



Review

Chronic Pain: Emerging Evidence for the Involvement of Epigenetics

Franziska Denk [1], Stephen B. McMahon [1]



Schematic Representation of the Key Processes Thought to Underlie Chronic Pain States

(A) Changes in brain function: a network of cortical and subcortical areas is involved in processing nociceptive signals and the sensation of pain.

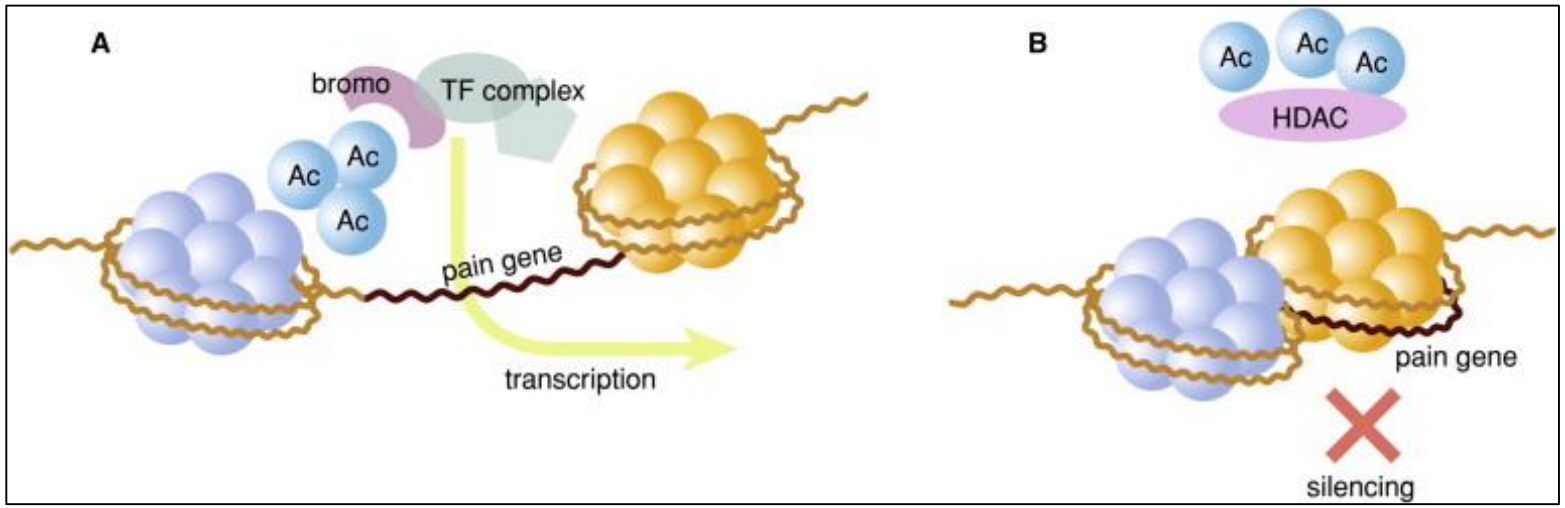
(B) Abnormal amplification of pain signals in DRG and spinal cord neurons: **sensory neurons display hyperexcitability as a result of altered neurotrophic support and extensive changes in the expression of relevant genes**, most notably ion channels and nociceptors. Second-order cells exhibit central sensitization as a result of several processes including immune and glial cell recruitment in the CNS.

(C) Peripheral inflammation and sensitization of nociceptors: tissue damage activates and recruits immune cells (e.g., mast cells, macrophages and neutrophils). These cells will release or stimulate the production of a variety of cytokines (e.g., IL-6, IL-1β, TNFα) and proinflammatory mediators (e.g., NGF and prostaglandins). This process will result in sensitization of the nociceptive neuron.

Review

Chronic Pain: Emerging Evidence for the Involvement of Epigenetics

Franziska Denk [1], Stephen B. McMahon [1]



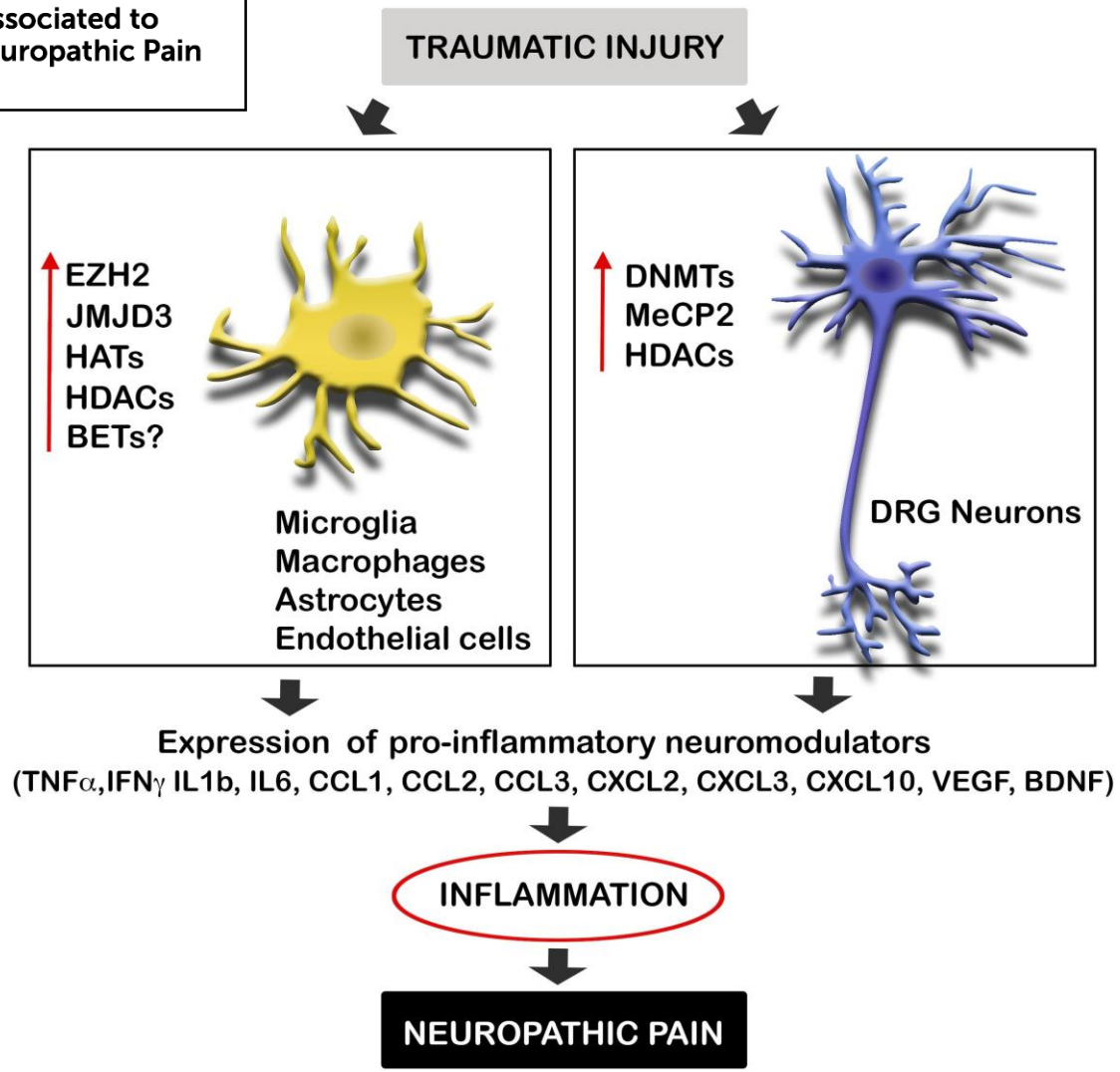
Schematic Illustrating One Possible Mechanism by which Epigenetic Processes Could Impact Development of Chronic Pain

(A) Acetylation at relevant nociceptive genes (Pain Gene, PG) could lead to a more open chromatin conformation through the negative charge of acetyl groups and the recruitment of transcription factor complexes (TF complex) containing bromodomain (bromo) readers. This would then lead to increased transcription of the genes in question, as is indeed observed in **chronic pain states**, where a large number of loci show abnormal upregulation.

(B) In contrast, in a **non pain state**, HDACs may be present to deacetylate the nociceptive promoters thus leaving the region in a heterochromatic, silenced state.

REVIEW ARTICLE
Front. Cell. Neurosci., 07 June 2018 | https://doi.org/10.3389/fncel.2018.00158

Epigenetic Modifications Associated to Neuroinflammation and Neuropathic Pain After Neural Trauma



Neuron
Review

Chronic Pain: Emerging Evidence for the Involvement of Epigenetics

Franziska Denk[1,*] and Stephen B. McMahon[1]
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DOI 10.1016/j.neuron.2012.01.012

Epigenetic processes, such as histone modifications and DNA methylation, have been associated with many neural functions including synaptic plasticity, learning, and memory. Here, we critically examine emerging evidence linking epigenetic mechanisms to the development or maintenance of chronic pain states. Although in its infancy, research in this area potentially unifies several pathophysiological processes underpinning abn

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Critical Review

Epigenetics: A Promising Paradigm for Better Understanding and Managing Pain

Seungmae Seo,* Adrienne Grzenda,* Gwen Lomberk,* Xiao-Ming Ou,[†]
Ricardo A. Cruciani,[‡,§,||] and Raul Urrutia*

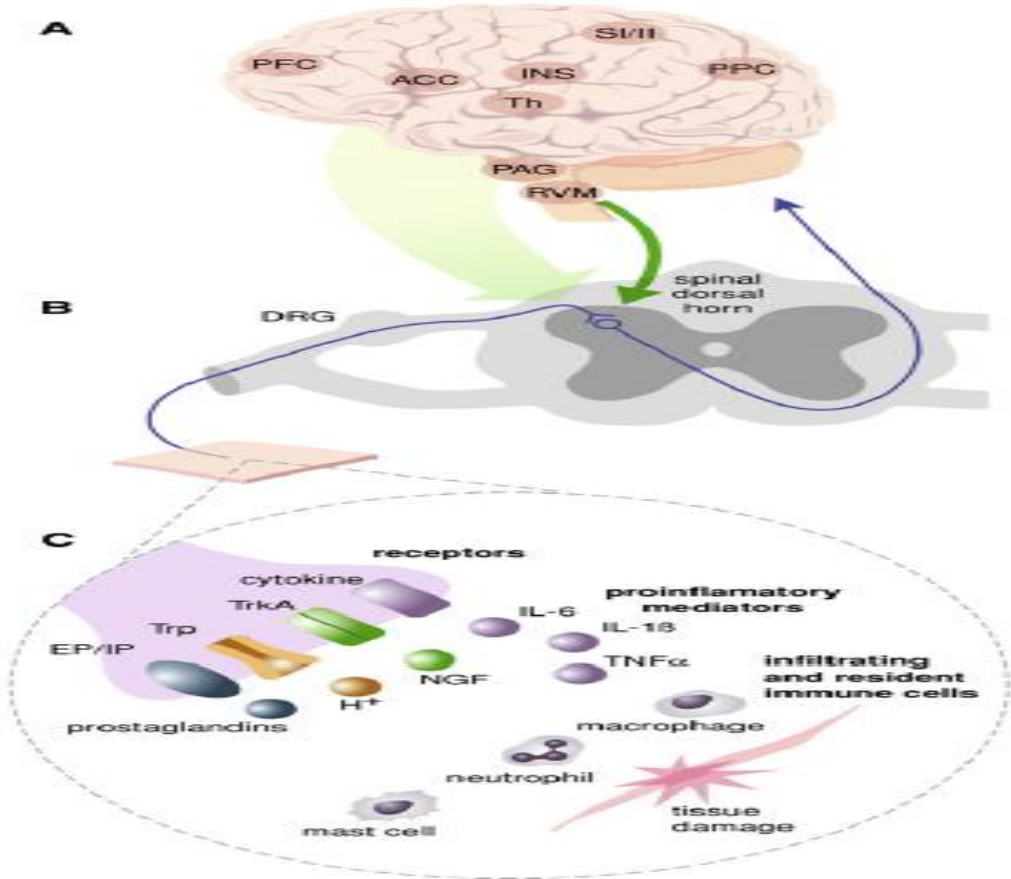


Figure 1. Schematic Representation of the Key Processes Thought to Underlie Chronic Pain States

(A) Changes in brain function: a network of cortical and subcortical areas is involved in processing nocioceptive signals and the sensation of pain (among others: prefrontal cortex [PFC], sensory motor cortices [SI/SII], posterior parietal cortex [PPC], anterior cingulate cortex [ACC], insula [INS], thalamus [Th], periaqueductal gray [PAG], and rostral ventromedial medulla [RVM]). In chronic pain patients, many of these display profound changes in fMRI bold signal, interconnectivity, and top-down modulation of ascending spinal signals.

(B) Abnormal amplification of pain signals in DRG and spinal cord neurons: sensory neurons display hyperexcitability as a result of altered neurotrophic support and extensive changes in the expression of relevant genes, most notably ion channels and nociceptors. Second-order cells exhibit central sensitization as a result of several processes including immune and glial cell recruitment in the CNS.

(C) Peripheral inflammation and sensitization of nocioceptors: tissue damage activates and recruits immune cells (e.g., mast cells, macrophages and neutrophils). These cells will release or stimulate the production of a variety of cytokines (e.g., IL-6, IL-1β, TNFα) and proinflammatory mediators (e.g., NGF and prostaglandins). This will activate or modulate the action of receptors on the sensory nerve terminals (e.g., the TrkA, cytokine, and prostaglandin

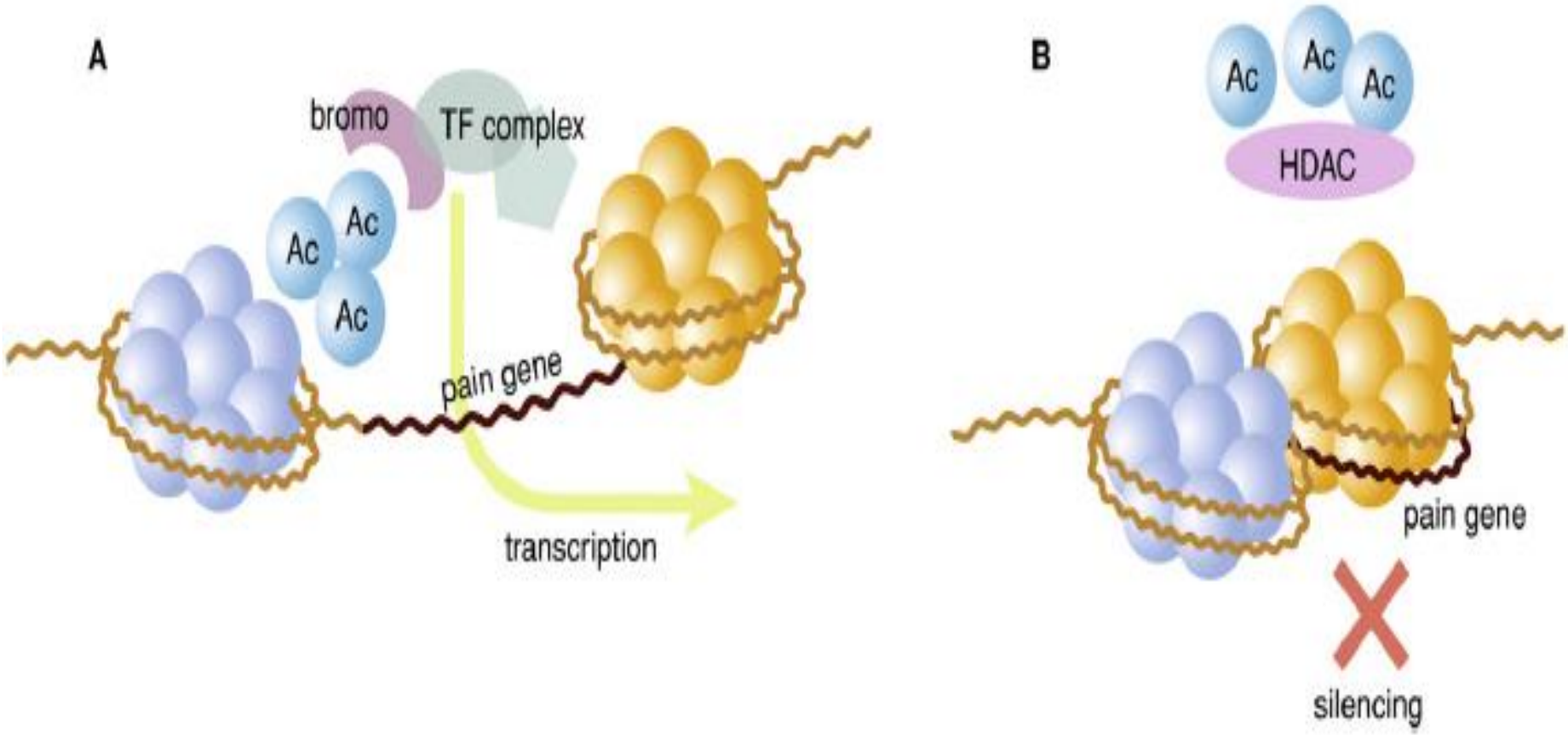


Figure 4. Schematic Illustrating One Possible Mechanism by which Epigenetic Processes Could Impact Development of Chronic Pain

(A) Acetylation at relevant nociceptive genes (Pain Gene, PG) could lead to a more open chromatin conformation through the negative charge of acetyl groups and the recruitment of transcription factor complexes (TF complex) containing bromodomain (bromo) readers. This would then lead to increased transcription of the genes in question, as is indeed observed in chronic pain states, where a large number of loci show abnormal upregulation (Lacroix-Fralish et al., 2011).

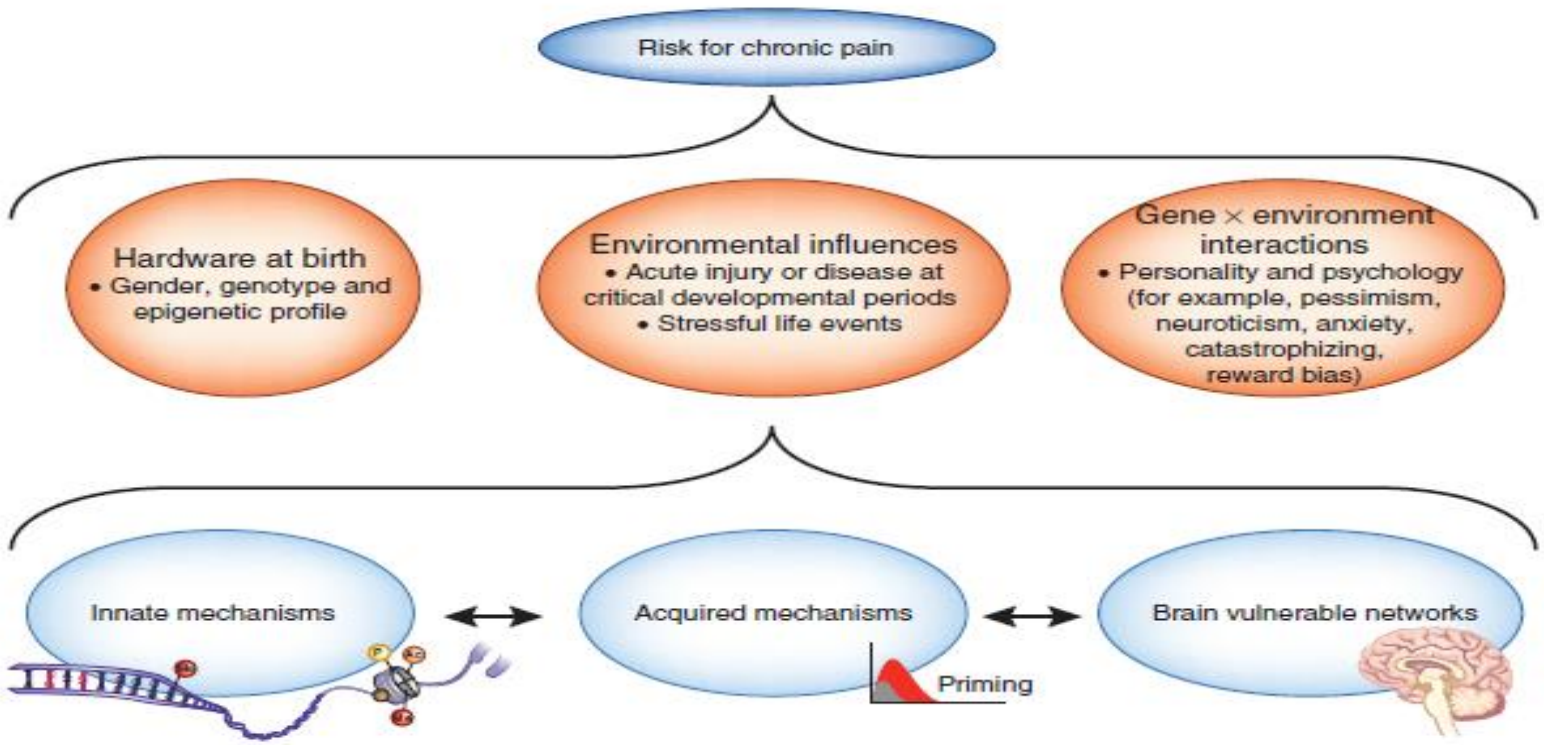
(B) In contrast, in a nonpain state, HDACs may be present to deacetylate the nociceptive promoters thus leaving the region in a heterochromatic, silenced state.

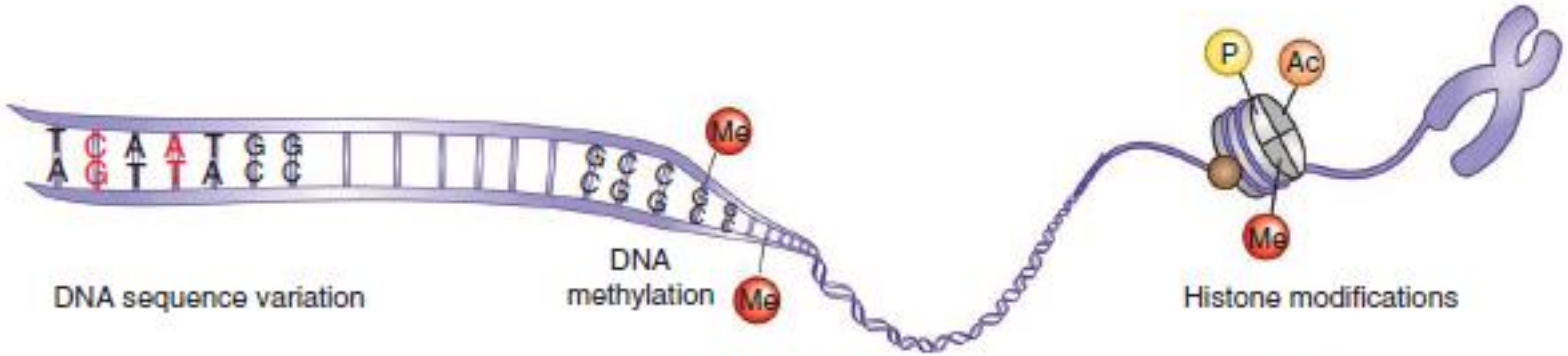
Pain vulnerability: a neurobiological perspective

nature neuroscience

Franziska Denk[1], Stephen B McMahon[1] & Irene Tracey[2]

There are many known risk factors for chronic pain conditions, yet the biological underpinnings that link these factors to abnormal processing of painful signals are only just beginning to be explored. This Review will discuss the potential mechanisms that have been proposed to underlie vulnerability and resilience toward developing chronic pain. Particular focus will be given to genetic and epigenetic processes, priming effects on a cellular level, and alterations in brain networks concerned with reward, motivation/learning and descending modulatory control. Although research in this area is still in its infancy, a better understanding of how pain vulnerability emerges has the potential to help identify individuals at risk and may open up new therapeutic avenues.





DNA sequence variation

DNA methylation

Histone modifications

Example: haplotype in *P2RX7* gene

Change in *P2RX7* pore formation

Osteoarthritis pain

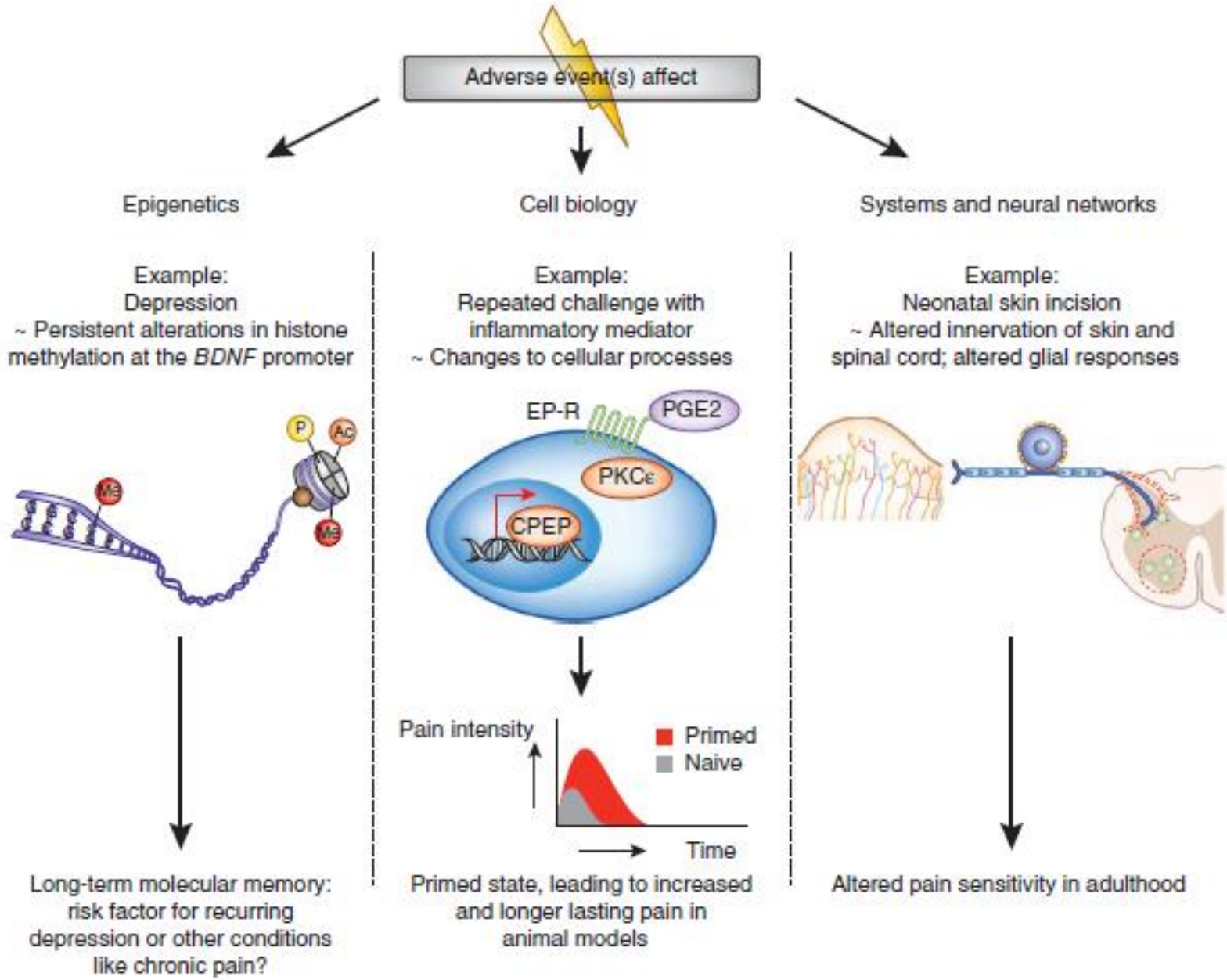
Example: DMR at *PARK2*
+
SNPs in *PARK2* gene

Lumbar disc degeneration

Example: HDAC inhibitors

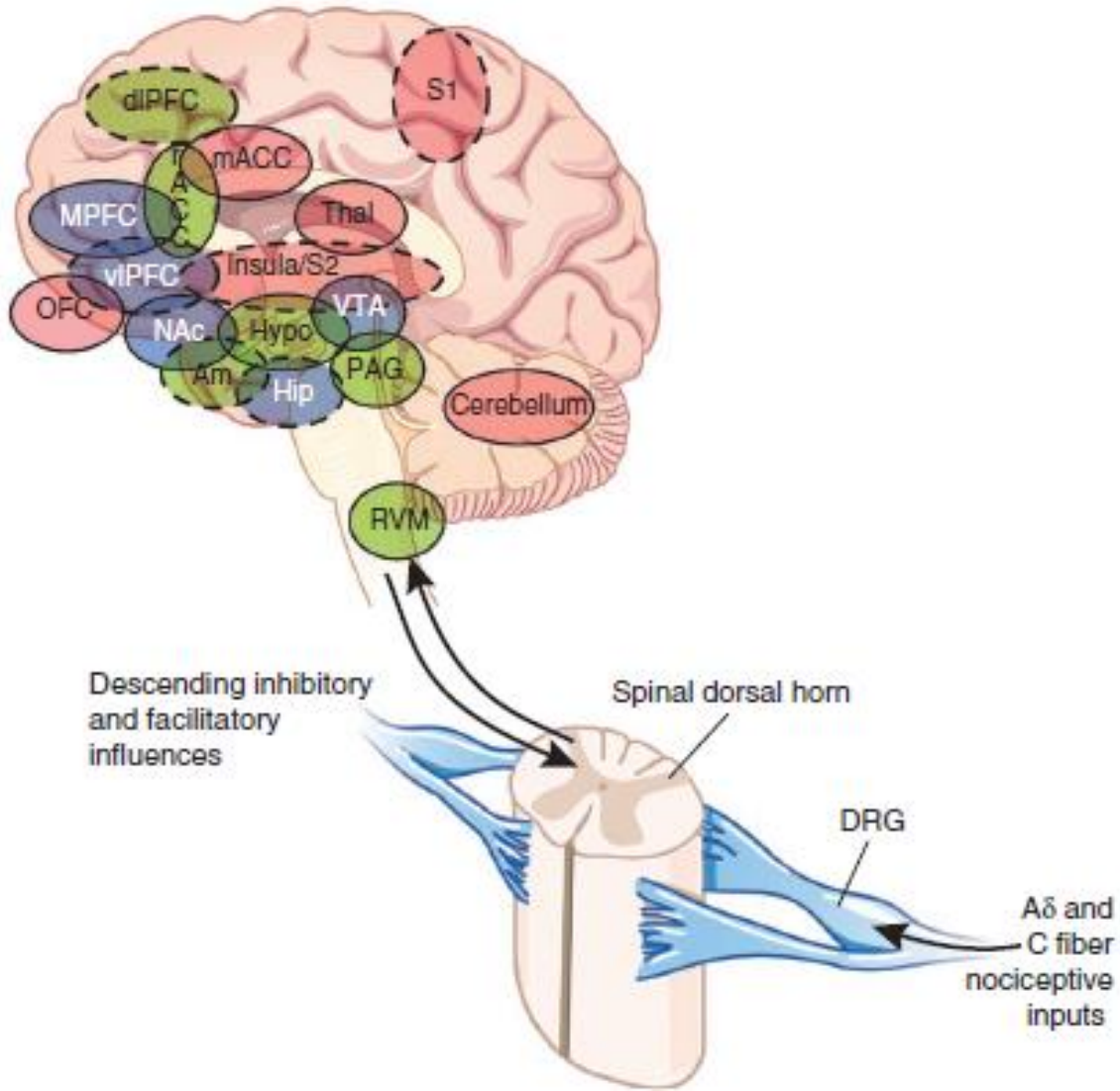
Transcriptional alterations

Analgesic effects in animal models of persistent pain


Adverse event(s) affect
Epigenetics
Cell biology
Systems and neural networks
Example:
Depression
~ Persistent alterations in histone methylation at the *BDNF* promoter
Example:
Repeated challenge with inflammatory mediator
~ Changes to cellular processes
Example:
Neonatal skin incision
~ Altered innervation of skin and spinal cord; altered glial responses
P
Ac
Me
Me
EP-R
PGE2
PKCε
CPEP
Pain intensity
Primed
Naive
Time
Long-term molecular memory: risk factor for recurring depression or other conditions like chronic pain?
Primed state, leading to increased and longer lasting pain in animal models
Altered pain sensitivity in adulthood

Networks with potential to affect risk for chronic pain

- Reward network
- DPMS
- Areas also relevant to pain percept but that might not affect risk



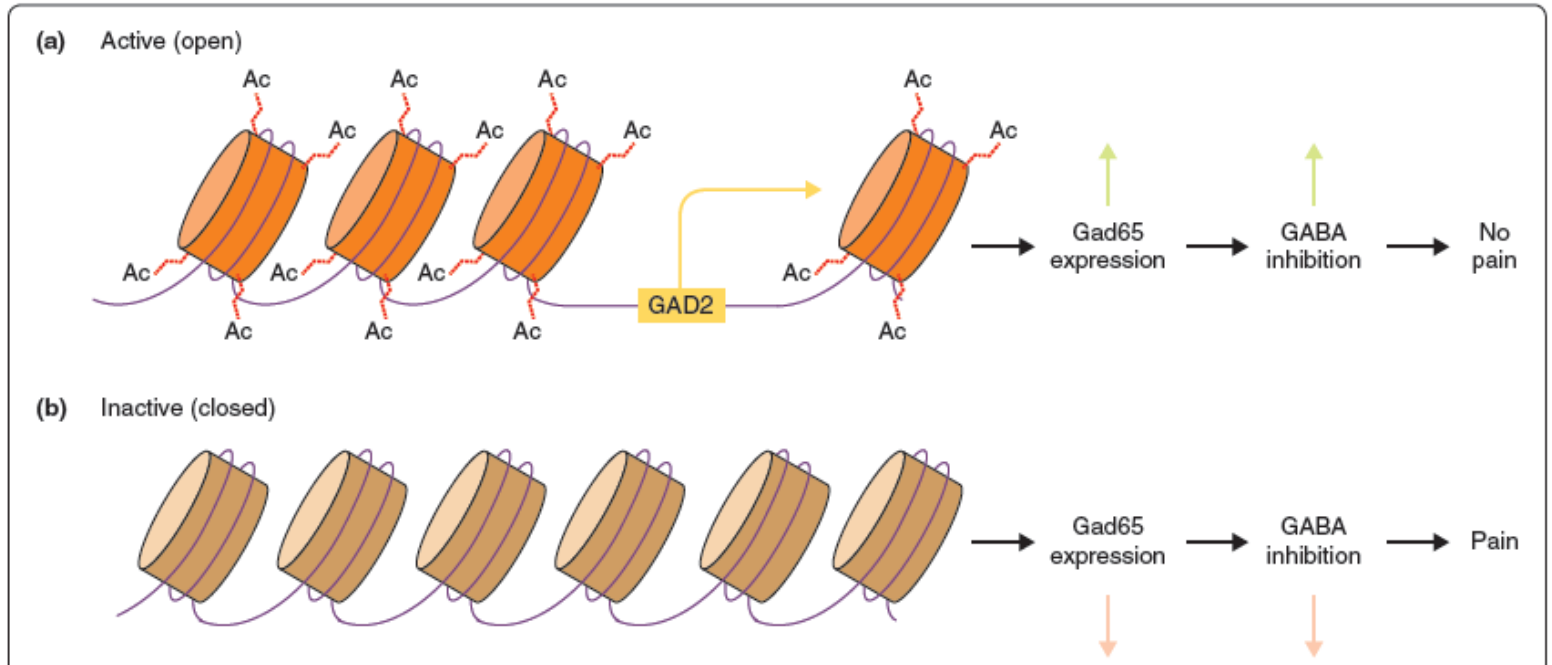


Figure 3. How epigenetic mechanisms can influence pain processing. **(a)** Under normal conditions, histone tails are acetylated at the *GAD2* promoter in the nucleus raphe magnus (NRM). **(b)** After application of complete Freund's adjuvant (CFA), Gad65 expression is suppressed through hypoacetylation of the GAD2 promoter, leading to loss of descending inhibition from the NRM [84]. GABA, γ-aminobutyric acid.

RESEARCH PAPER

HDAC inhibitors restore C-fibre sensitivity in experimental neuropathic pain model

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Keywords
epigenetics; HDAC inhibitor; $Na_v1.8$; hypoesthesia; neuropathic pain

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Review

Multiple roles of HDAC inhibition in neurodegenerative conditions

De-Maw Chuang, Yan Leng, Zoya Marinova, Hyeon-Ju Kim and Chi-Tso Chiu

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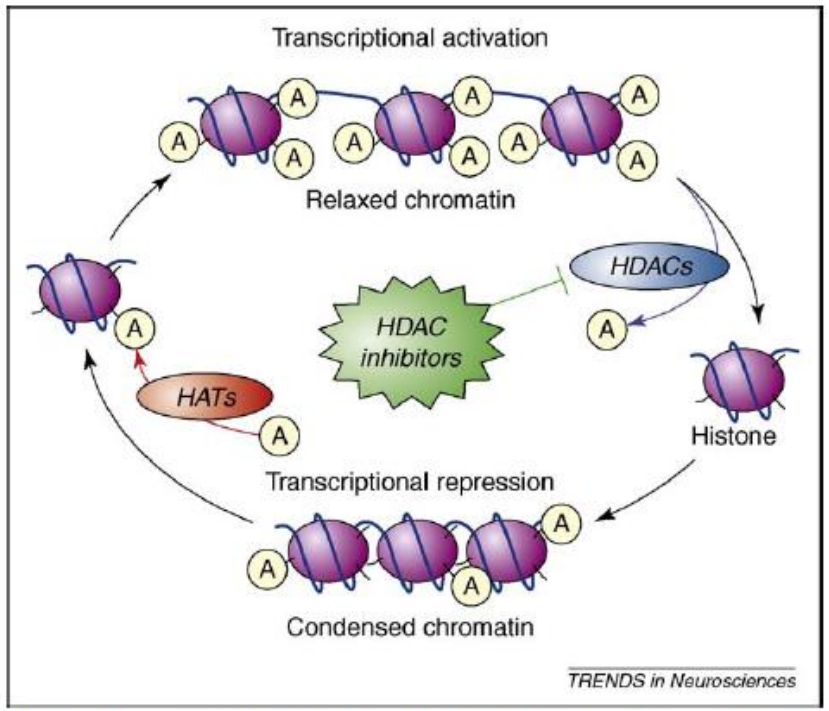
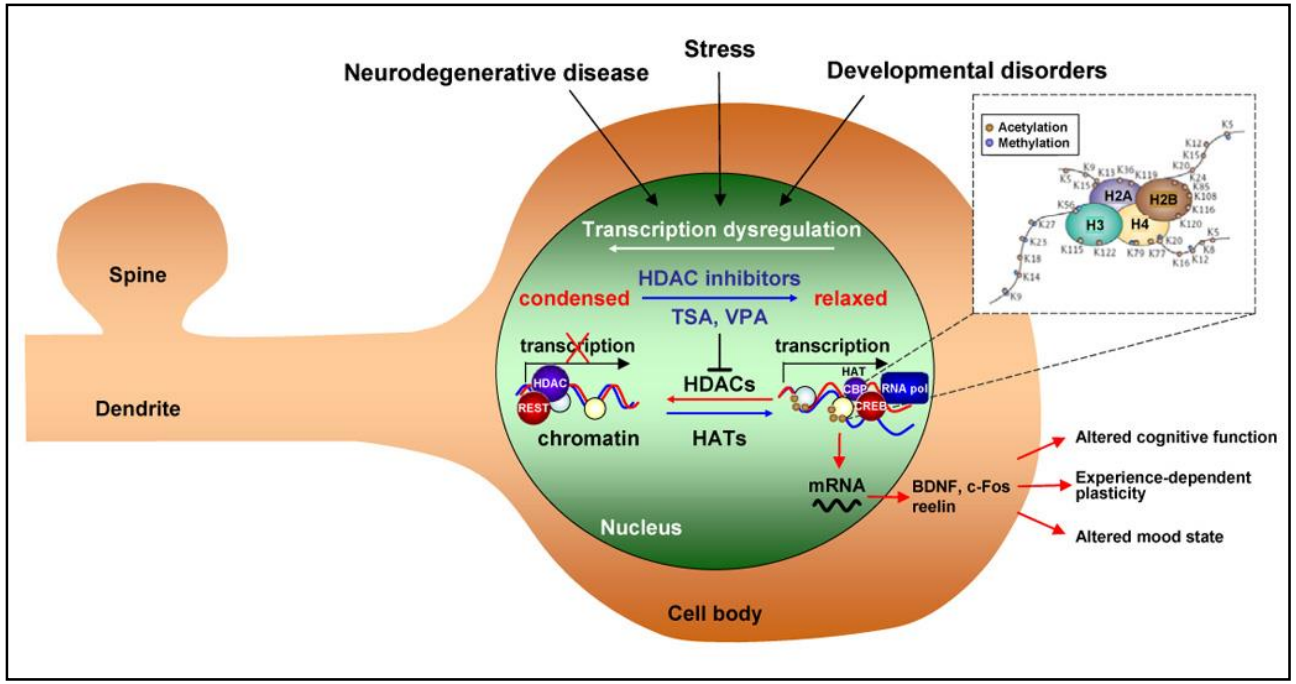


Figure 1. Effects of HDAC inhibitors on chromatin remodeling. Levels of histone acetylation at Lys residues on histone-tails are determined by interplays of acetylation and deacetylation catalyzed by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. Inhibition of HDACs by HDAC inhibitors results in a net increase in histone acetylation levels and a more open, relaxed chromatin conformation that favors transcriptional activation. By contrast, chromatin with a compact conformation is transcriptionally inactive. Ⓐ, acetylated Lys residues of histone-tail proteins.

Curr Opin Pharmacol. 2008 Feb;8(1):57-64. doi: 10.1016/j.coph.2007.12.002.

Epigenetic targets of HDAC inhibition in neurodegenerative and psychiatric disorders.



Scheme showing that neurological and psychiatric disorders involve epigenetic modifications of key neuronal genes and intervention by HDAC inhibitors

Neurodegenerative diseases (Huntington's disease, Parkinson's disease and ischemia), psychiatric disorders (depression, stress and anxiety) and neurodevelopmental disorders can involve **aberrant acetylation and methylation of histones and/or DNA methylation**. These epigenetic modifications can be influenced by experience and determine the transcriptional state of regulatory genes critical to synaptic plasticity, cognition and mood. **Histone deacetylase inhibitors amelioration of plasticity and cognitive deficits.**

J Neurochem. 2015 Aug;134(4):642-51. doi: 10.1111/jnc.13171. Epub 2015 Jun 4.

Hippocampal chromatin-modifying enzymes are pivotal for scopolamine-induced synaptic plasticity gene expression changes and memory impairment.

Scopolamine administration drastically up-regulated DNA methyltransferases (DNMT1) and HDAC2 expression. HDAC inhibitor sodium butyrate and DNMT inhibitor Aza-20deoxycytidine recovered scopolamine-impaired hippocampal-dependent memory consolidation with concomitant increase in the expression of synaptic plasticity genes Brain-derived neurotrophic factor (BDNF) and Arc and level of histone H3K9 and H3K14 acetylation and decrease in DNA methylation level.

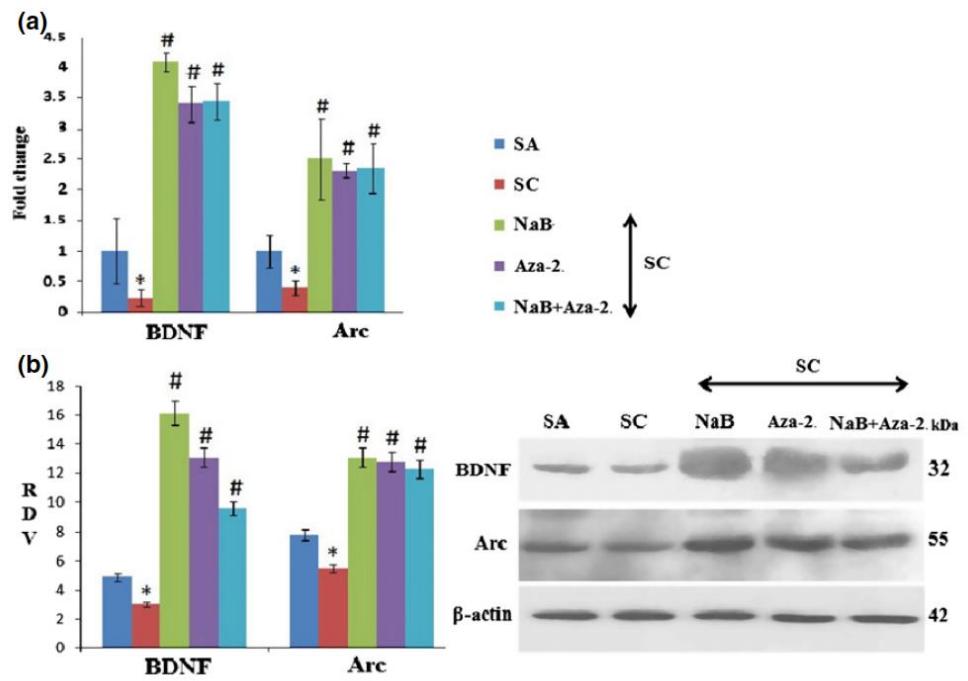


Fig. 2 (a) Quantitative real-time PCR of BDNF and Arc expression in scopolamine (SC)-treated mice as compared to saline control (SA) and Sodium butyrate (NaB), Aza-2′deoxycytidine (Aza-2) and NaB+Aza-2-treated mice. (b) Western blot analysis of BDNF and Arc proteinexpression. Histogram represents relative density value (RDV) (IDV of BDNF/Arc/IDV of β-Actin) from three independent experiments. Data are represented as Mean ± SEM and '*' and '#' denote significant differences ($p < 0.05$) as compared to SA and SC, respectively (one-way ANOVA followed by Tukey's test).

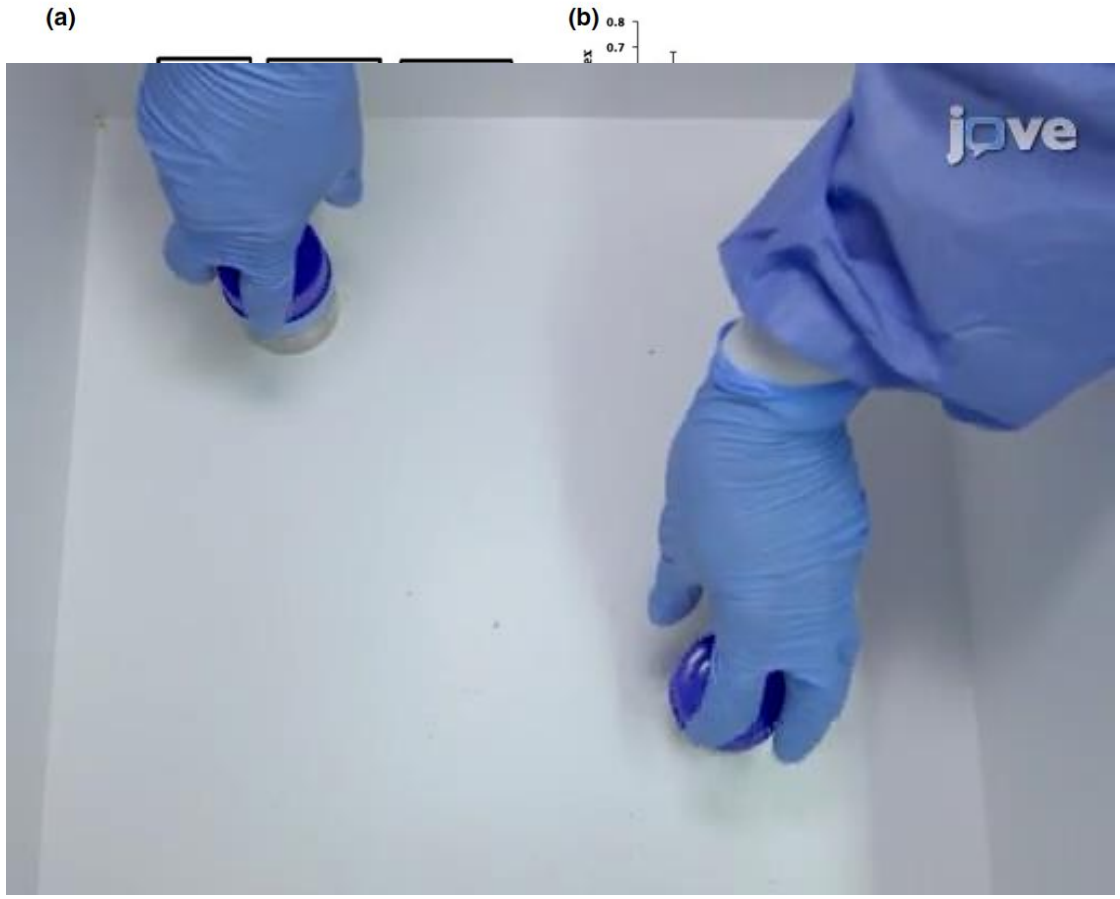
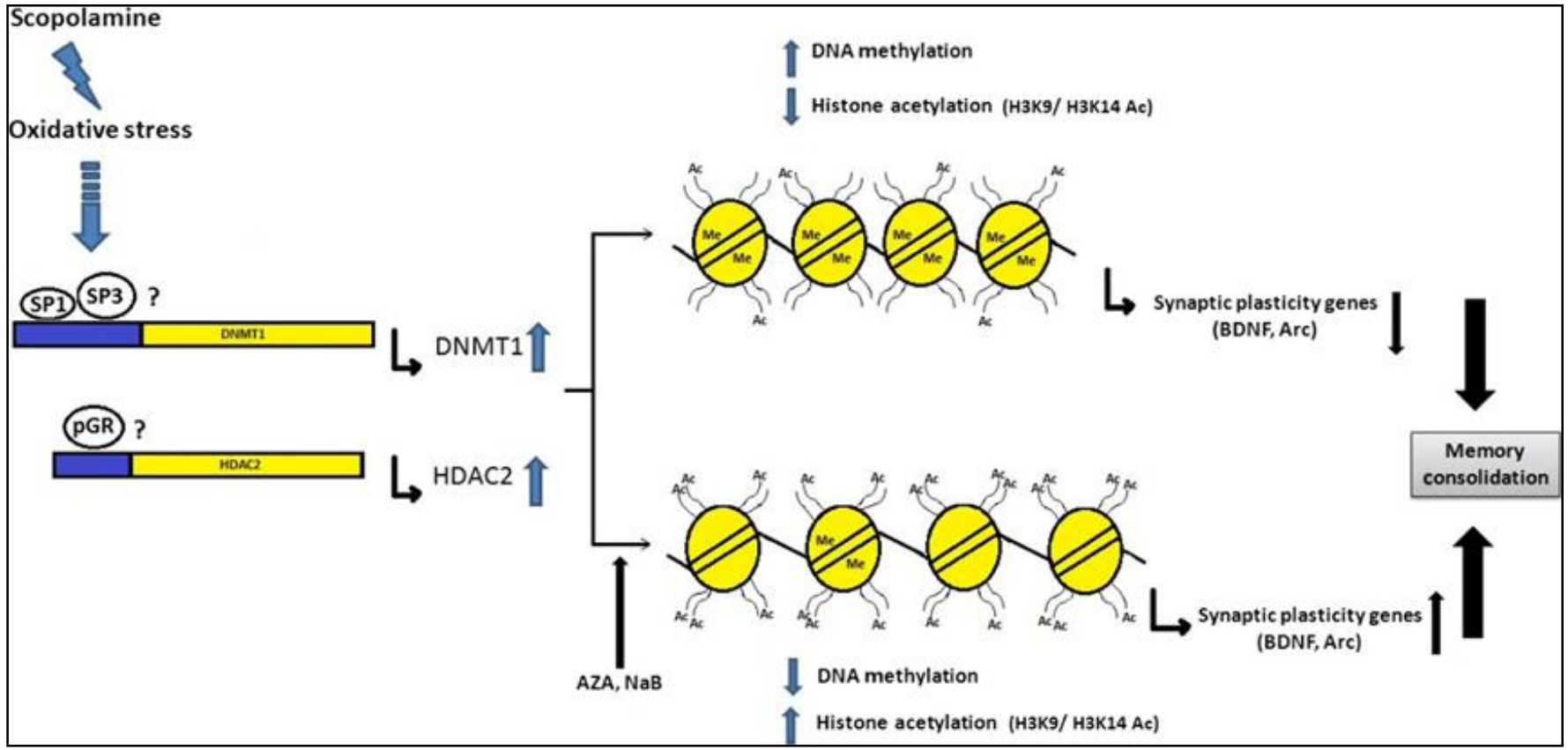
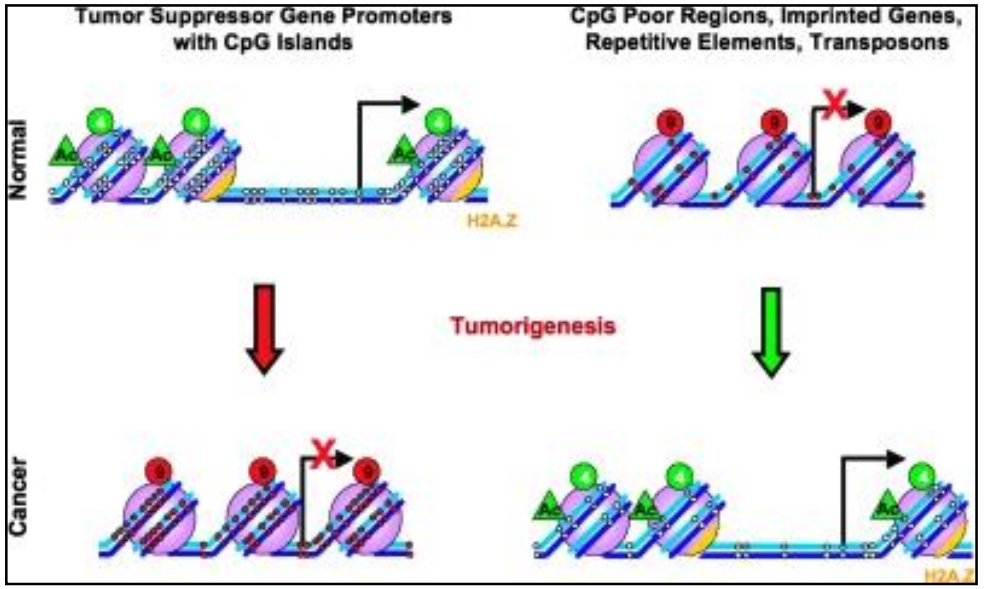


Fig. 3 Effect of HDAC inhibitor Sodium butyrate (NaB) and DNA methyltransferases (DNMT) inhibitor Aza-2′deoxycytidine (Aza-2) on novel object recognition memory test, histone acetylation and DNA methylation level in scopolamine (SC)-treated mice. (a) Experimental design: mice were treated with respective drug for 7 days. On 5th and 6th day, mice were habituated in the open box. On 7th day, two similar objects were placed in the box and mice were allowed to interact. On 8th day, one object was replaced by novel one and mice were allowed to interact with both the objects (b) Discrimination index (DI). (c) Western blot analysis showing protein expression and histogram represents relative density value (RDV) (IDV of HDAC2/H3K9 Ac/H3K14 Ac/IDV of H3). (d) Chromatin immunoprecipitation analysis showing histone acetylation level at the promoter of BDNF and Arc. (e) Methylated DNA immunoprecipitation (MeDIP) analysis showing DNA methylation level at the promoter of BDNF and Arc. Data are represented Mean ± SEM. '*' and '#' denote significant differences ($p < 0.05$) as compared to SA and SC, respectively (one-way ANOVA followed by Tukey's test).


Scopolamine
Oxidative stress
SP1
SP3
?
DNMT1
DNMT1
pGR
?
HDAC2
HDAC2
AZA, NaB
DNA methylation
Histone acetylation (H3K9/ H3K14 Ac)
Synaptic plasticity genes (BDNF, Arc)
Memory consolidation
Synaptic plasticity genes (BDNF, Arc)
DNA methylation
Histone acetylation (H3K9/ H3K14 Ac)

DNA methylation changes in cancer

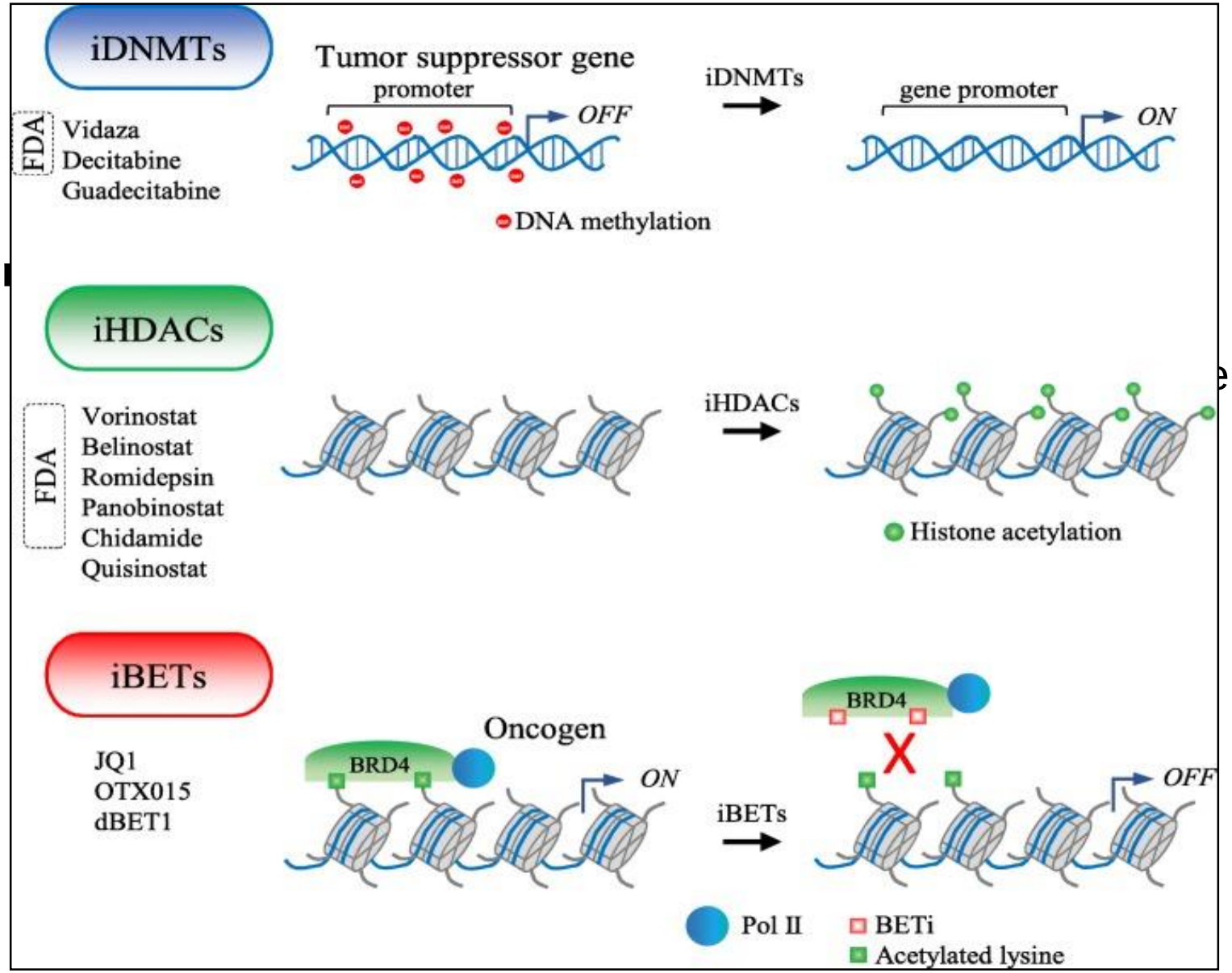


Epigenetics in cancer

Shikhar Sharma,[1,2] Theresa K. Kelly,[1] and Peter A. Jones[1,*]

In normal cells, CpG island promoters are generally unmethylated and when active, as in the case of tumor suppressor genes, are accompanied by active histone marks such as acetylation and H3K4 methylation (green circles, 4) allowing for a transcriptionally active open chromatin structure.
However, repetitive regions, transposons, CpG poor intergenic regions and imprinted gene promoters are heavily methylated and accompanied by repressive histone marks such as H3K9 methylation (red circles, 9) that together form a silent chromatin state. **During tumorigenesis, tumor suppressor gene promoters with CpG islands become methylated, resulting in the formation of silent chromatin structur**e and aberrant silencing (indicated by the red arrow). In contrast, the repetitive sequences, transposons and imprinted gene promoters become hypomethylated resulting in their aberrant activation (indicated by the green arrow).

EPIGENETIC and Cancer



Disease model	Histone hypo-acetylation/ transcriptional dysfunction	Microtubule dysfunction	HDAC inhibitors examined	Beneficial effects after treatment
Stroke	Yes	Yes	Valproic acid, vorinostat, sodium butyrate, TSA, 4-phenylbutyrate	Restored histone hypoacetylation and transcriptional dysfunction; enhanced neurogenesis; decreased infarct volume, neuroinflammation and neurological deficits
Huntington's disease (HD)	Yes	Yes	Vorinostat, sodium butyrate, 4-phenylbutyrate, TSA, HDACi 4b, nicotinamide	Restored histone hypoacetylation and transcriptional dysfunction; normalized striatal atrophy and degeneration; increased BDNF vesicular transport; improved motor performance and survival
Amyotrophic lateral sclerosis (ALS)	Yes	?	4-Phenylbutyrate, valproic acid, 4-phenylbutyrate+antioxidant, valproic acid+lithium, 4-phenylbutyrate+riluzole	Restored histone hypoacetylation and CBP loss; suppressed motor neuronal death; improved motor function and survival
Spinal muscular atrophy (SMA)	Yes	?	Sodium butyrate, 4-phenylbutyrate, valproic acid, vorinostat, TSA, romidepsin (FK-228)	Increased SMN_2 expression; induced Bcl-2, Bcl-X_L and BDNF; suppressed spinal motor neuronal degeneration and muscle atrophy; prolonged life span
Parkinson's disease (PD)	Yes	Yes	Valproic acid, sodium butyrate, TSA, vorinostat, AGK2	Increased GDNF and BDNF expression; reduced neuroinflammation and dopaminergic neuronal death; increased acetylation of α-tubulin
Alzheimer's disease (AD)	Yes	Yes	Valproic acid, sodium butyrate, 4-phenylbutyrate, nicotinamide, vorinostat	Restored histone hypoacetylation; increased synaptic plasticity; decreased Aβ production and *Tau* hyperphosphorylation; reinstated learning and memory; reversed spatial memory deficits

HDAC inhibitors currently under clinical investigation.

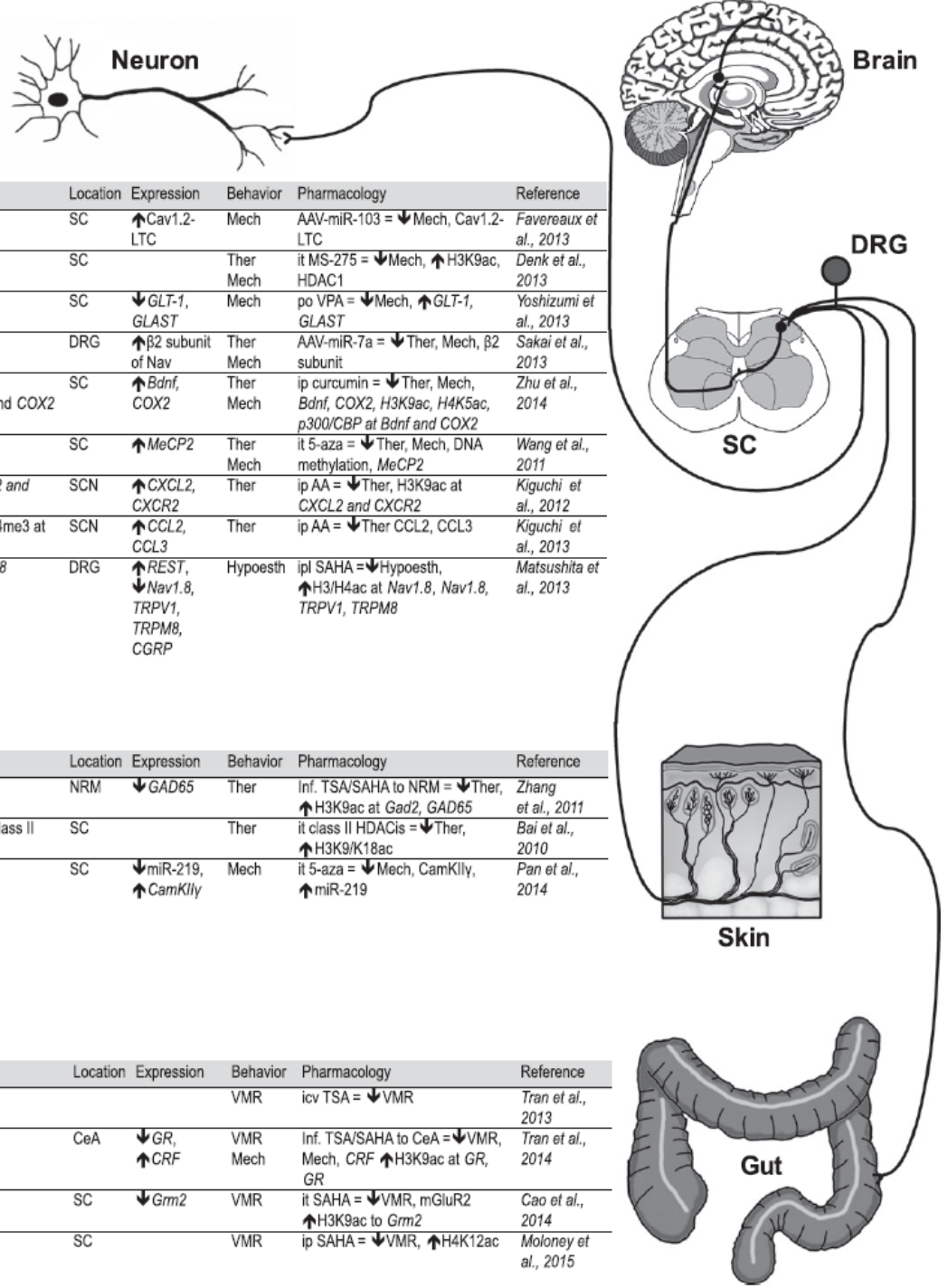
Group	Compound	HDAC target[1]	Current state
Hydroxamic acid	Vorinostat (SAHA, Zolinza)	class I, II, IV	FDA approved
	Panobinostat (LBH589)	class I, II, IV	phase III CT
	Belinostat (PXD101)	class I, II, IV	phase II CT
	Abexinostat (PCI24781)	class I, II	phase II CT
	Resminostat (RAS2410)	class I, II	phase II CT
	Givinostat (ITF2357)	class I, II	phase II CT
	Dacinostat (LAQ824, NVP-LAQ824)	class I, II	phase I CT
	Pracinostat (SB939)	class I, II	phase II CT
Cyclic tetrapeptide	Romidepsin (Depsipeptide, FK228)	HDAC1, 2	FDA approved
	Apicidin	HDAC2, 3	Phase II CT
	Trapoxin A	HDAC1, 4, 11	ND[2]
Benzamide	Mocetinostat (MGCD0103)	HDAC1, 2, 11	phase II CT
	Entinostat (MS-275, SNDX-275)	HDAC1, 9, 11	phase II CT
	Rocilinostat (ACY-1215)	HDAC6	phase II CT
Aliphatic acid	Valproic acid (VPA)	class I	phase III CT
	Pivanex (AN-9)	ND	phase II CT
	Butyrate	class I, IIa	Phase II CT
Electrophilic ketone	Trifluorometchylketone	ND	ND

most inhibitors are at different stages of clinical trials, **SAHA and depsipeptide have been approved by FDA for cancer chemotherapeutic intervention.**

SNL spinal nerve ligation
CCI chronic constriction injury
PSNL partial sciatic nerve ligation

CFA complete Freund's adjuvant

WAS water avoidance stress
CORT corticosterone
E2 estradiol
MS, maternal separation



Neuropathic Pain

Model	Mark/Enzyme	Location	Expression	Behavior	Pharmacology	Reference
SNL	↓miR-103	SC	↑Cav1.2-LTC	Mech	AAV-miR-103 = ↓Mech, Cav1.2-LTC	*Favereaux et al., 2013*
SNL		SC		Ther Mech	it MS-275 = ↓Mech, ↑H3K9ac, HDAC1	*Denk et al., 2013*
SNL		SC	↓*GLT-1, GLAST*	Mech	po VPA = ↓Mech, ↑*GLT-1, GLAST*	*Yoshizumi et al., 2013*
SNL/ CCI	↓miR-7a	DRG	↑β2 subunit of Nav	Ther Mech	AAV-miR-7a = ↓Ther, Mech, β2 subunit	*Sakai et al., 2013*
CCI	↑H3K9ac, H4K5ac, p300/CBP at *Bdnf* and *COX2*	SC	↑*Bdnf, COX2*	Ther Mech	ip curcumin = ↓Ther, Mech, *Bdnf, COX2, H3K9ac, H4K5ac, p300/CBP at Bdnf and COX2*	*Zhu et al., 2014*
CCI	↑DNA methylation	SC	↑*MeCP2*	Ther Mech	it 5-aza = ↓Ther, Mech, DNA methylation, *MeCP2*	*Wang et al., 2011*
PSNL	↑H3K9ac at *CXCL2 and CXCR2*	SCN	↑*CXCL2, CXCR2*	Ther	ip AA = ↓Ther, H3K9ac at *CXCL2 and CXCR2*	*Kiguchi et al., 2012*
PSNL	↑H3K9ac and H3K4me3 at *CCL2 and CCL3*	SCN	↑*CCL2, CCL3*	Ther	ip AA = ↓Ther CCL2, CCL3	*Kiguchi et al., 2013*
PSNL	↓H3/H4ac at *Nav1.8*	DRG	↑*REST*, ↓*Nav1.8, TRPV1, TRPM8, CGRP*	Hypoesth	ipl SAHA =↓Hypoesth, ↑H3/H4ac at *Nav1.8, Nav1.8, TRPV1, TRPM8*	*Matsushita et al., 2013*

Somatic Pain

Model	Mark/Enzyme	Location	Expression	Behavior	Pharmacology	Reference
CFA	↓H3K9ac at *Gad2*	NRM	↓*GAD65*	Ther	Inf. TSA/SAHA to NRM = ↓Ther, ↑H3K9ac at *Gad2, GAD65*	*Zhang et al., 2011*
CFA	↓H3K9/K18ac, ↑class II HDACs	SC		Ther	it class II HDACis = ↓Ther, ↑H3K9/K18ac	*Bai et al., 2010*
CFA	↑DNA methylation	SC	↓miR-219, ↑*CamKIIγ*	Mech	it 5-aza = ↓Mech, CamKIIγ, ↑miR-219	*Pan et al., 2014*

Visceral Pain

Model	Mark/Enzyme	Location	Expression	Behavior	Pharmacology	Reference
WAS				VMR	icv TSA = ↓VMR	*Tran et al., 2013*
CORT	↓H3K9ac at *GR*	CeA	↓*GR*, ↑*CRF*	VMR Mech	Inf. TSA/SAHA to CeA =↓VMR, Mech, *CRF* ↑H3K9ac at *GR, GR*	*Tran et al., 2014*
E2	↓H3ac	SC	↓*Grm2*	VMR	it SAHA = ↓VMR, mGluR2 ↑H3K9ac to *Grm2*	*Cao et al., 2014*
MS	↓H4K12ac	SC		VMR	ip SAHA = ↓VMR, ↑H4K12ac	*Moloney et al., 2015*

Neuropathic pain

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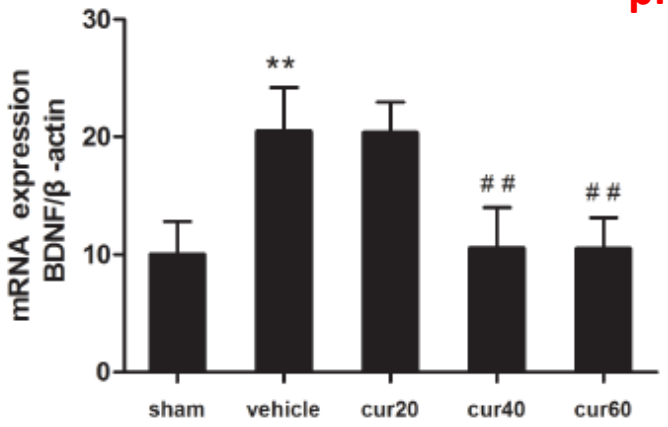
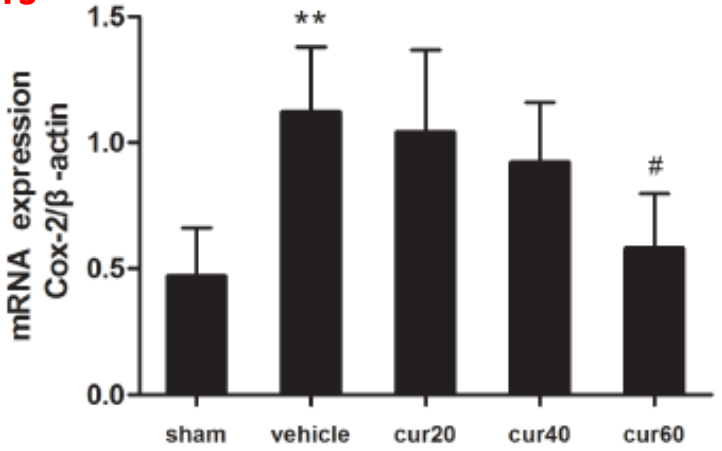
PLOS ONE

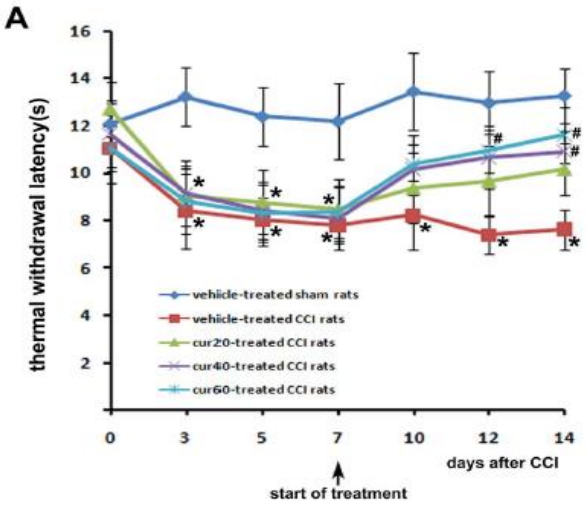
Curcumin Alleviates Neuropathic Pain by Inhibiting p300/CBP Histone Acetyltransferase Activity-Regulated Expression of BDNF and Cox-2 in a Rat Model

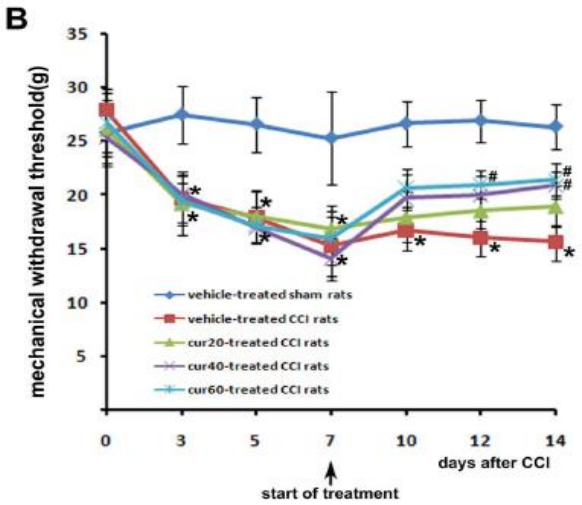
pro-nociceptive factors



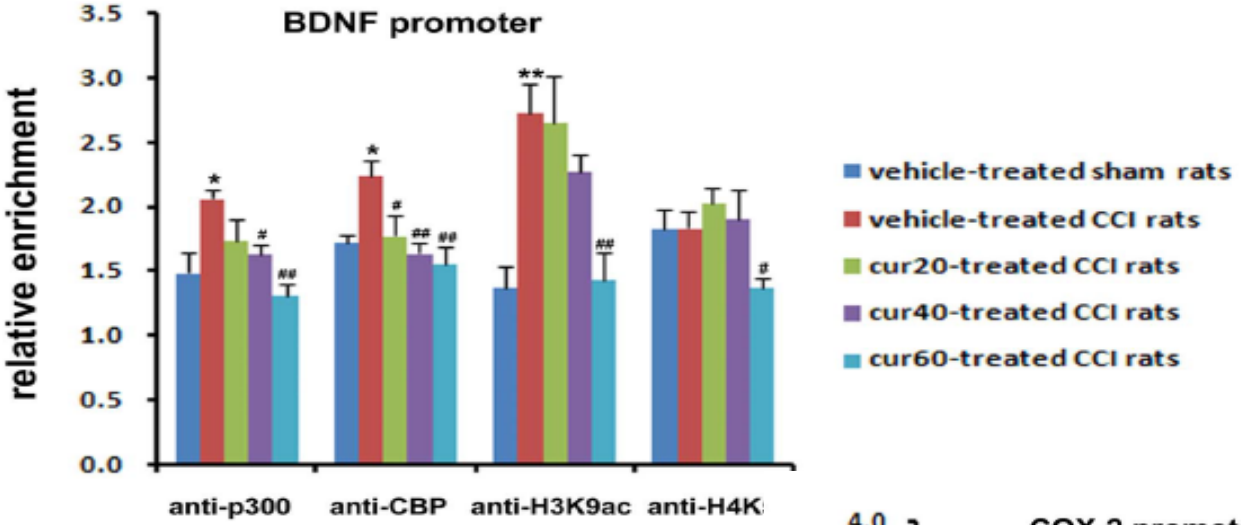


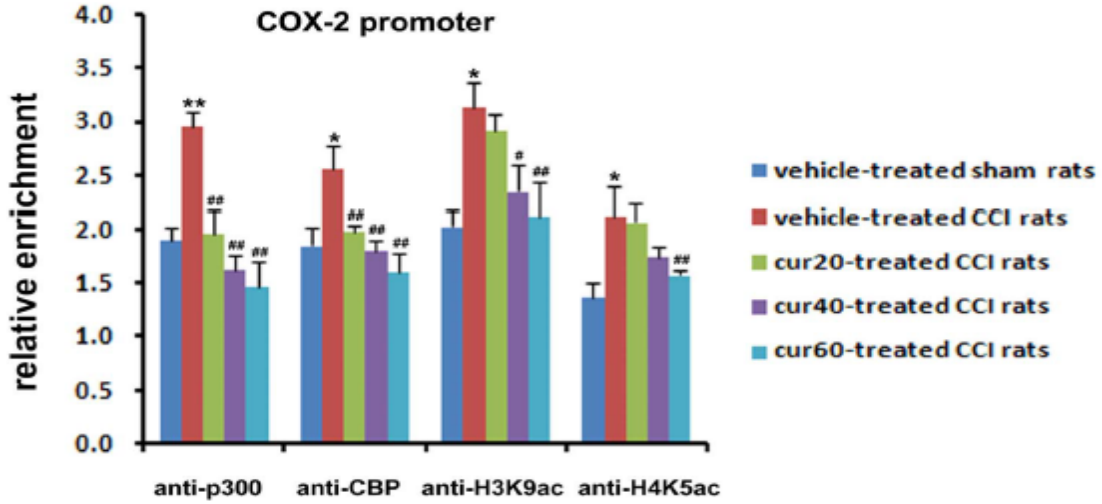
Thermal hyperalgesia





Mechanical allodynia





The management of neuropathic pain is still
treatments. Curcumin has been reported to play
neuropathic pain. Curcumin has long been r
acetyltransferase (HAT) activity. However, this m
pain with curcumin. The aim of the present stu
constriction injury (CCI) rat model of neuropathic
on P300/CBP HAT activity-regulated release of the pro-nociceptive molecules, brain-derived neurotrophic factor (BDNF) and cyclooxygenase-2 (Cox-2). Treatment with 40 and 60 mg/kg body weight curcumin for 7 consecutive days significantly attenuated CCI-induced thermal hyperalgesia and mechanical allodynia, whereas 20 mg/kg curcumin showed no significant analgesic effect. Chromatin immunoprecipitation analysis revealed that curcumin dose-dependently reduced the recruitment of p300/CBP and acetyl-Histone H3/acetyl-Histone H4 to the promoter of BDNF and Cox-2 genes. A similar dose-dependent decrease of BDNF and Cox-2 in the spinal cord was also observed after curcumin treatment. These results indicated that curcumin exerted a therapeutic role in neuropathic pain by down-regulating p300/CBP HAT activity-mediated gene expression of BDNF and Cox-2.

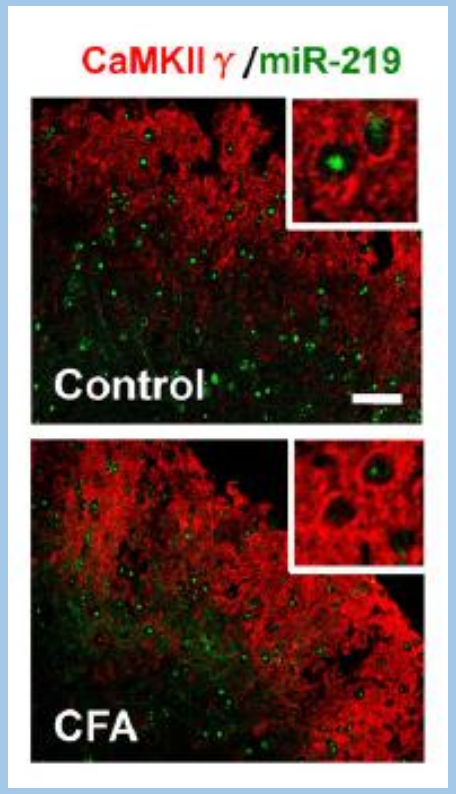
Somatica Pain

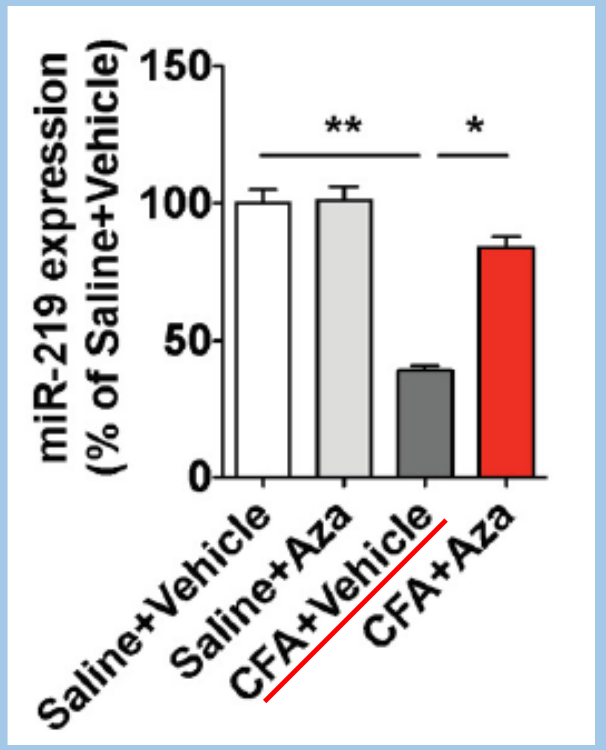
Inflammation induces epigenetic modifications: both by dysregulation of **HATs/HDACs** and also by **DNA hypermethylation**

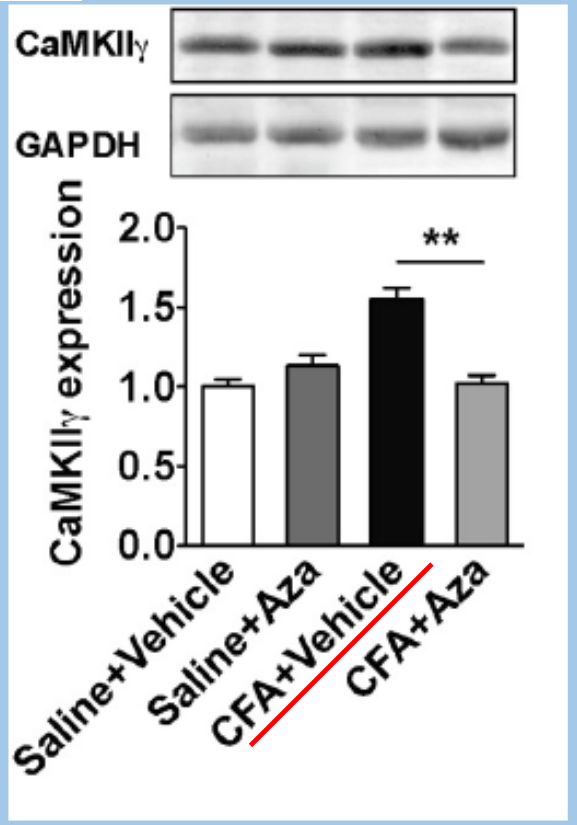
Azacytidine = demethylant agent
5'-aza-2'

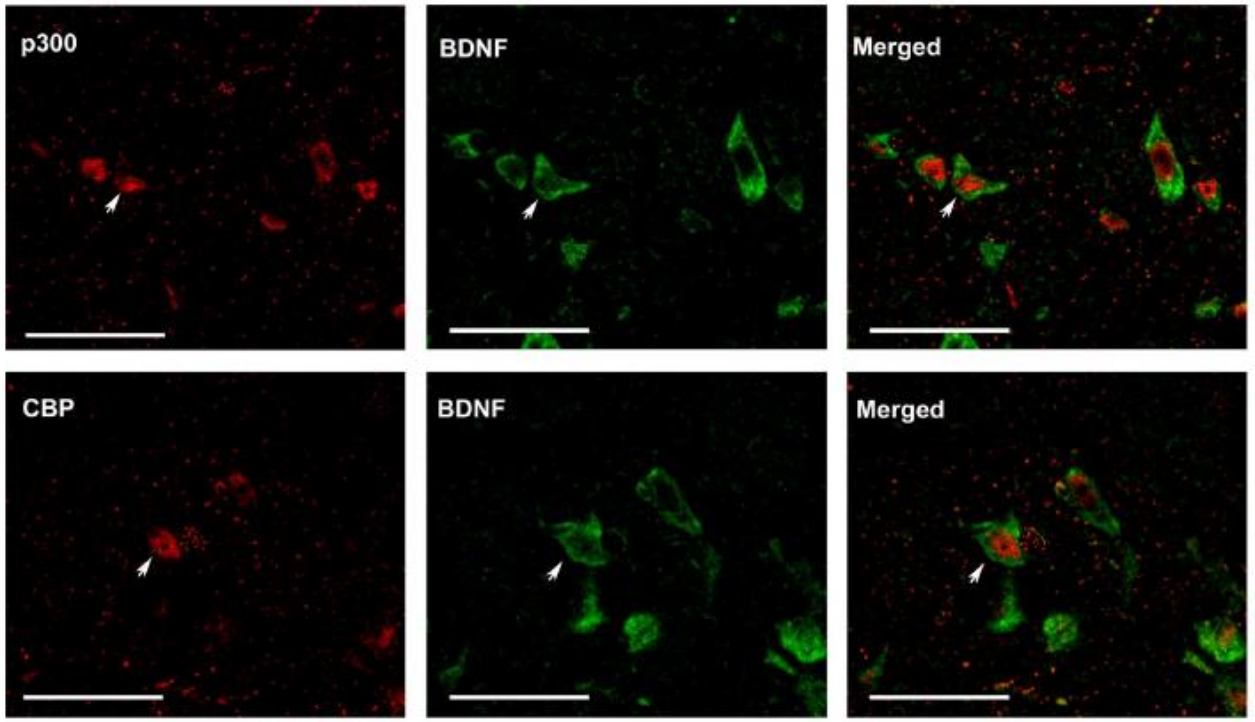
Neurobiology of Disease

Epigenetic Modification of Spinal miR-219 Expression Regulates Chronic Inflammation Pain by Targeting CaMKIIγ





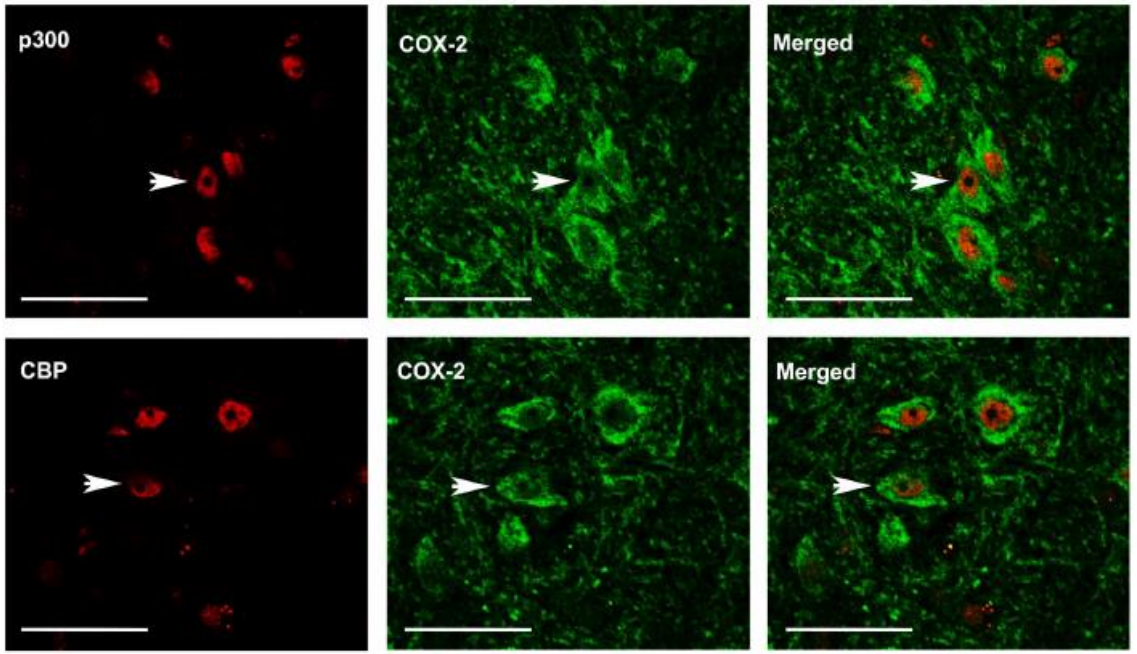




ipsilateral spinal dorsal horn of CCI rats

Double immunofluorescence staining of

p300/CREB binding protein (CBP) and BDNF or COX2



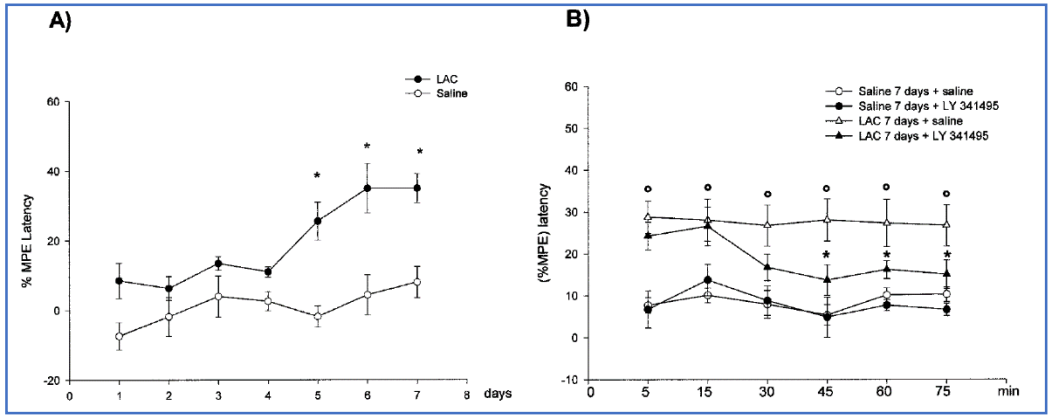
Mol Pharmacol. 2002 May;61(5):989-96.

L-Acetylcarnitine induces analgesia by selectively up-regulating mGlu2 metabotropic glutamate receptors.

Chiechio S[1], Caricasole A, Barletta E, Storto M, Catania MV, Copani A, Vertechy M, Nicolai R, Calvani M, Melchiorri D, Nicoletti F.

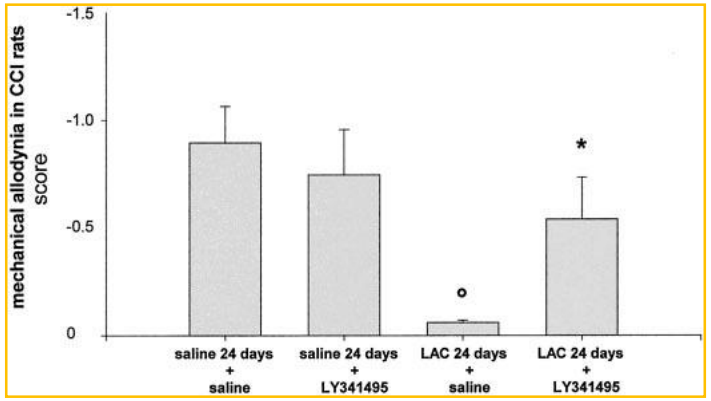
Analgesic Activity of LAC

Repeated injections of LAC (100 mg/kg, s.c., twice daily for 7 days) induced thermal analgesia in intact rats, as reflected by an increased latency in the plantar test.



A, repeated injections of LAC (100 mg/kg, s.c., twice daily) induces analgesia in intact rats subjected to an acute **thermal stimulation in the plantar test**. Note that a treatment with LAC of at least 5 days is required for the induction of analgesia. Data are means S.E.M. from six animals and are expressed as percentage of maximum possible effect (%MPE) .
B, a single injection of LY 341495 (1 mg/kg, i.p.) reduces LAC-induced analgesia in a time-dependent manner.

The analgesic effect of a 24-day treatment with LAC was prevented by a single injection of LY 341495 (1 mg/kg, i.p.) a potent and systemically active mGlu2/3 receptor antagonist.
LY 341495 did not affect allodynia in CCI rats that had not been treated with LAC.

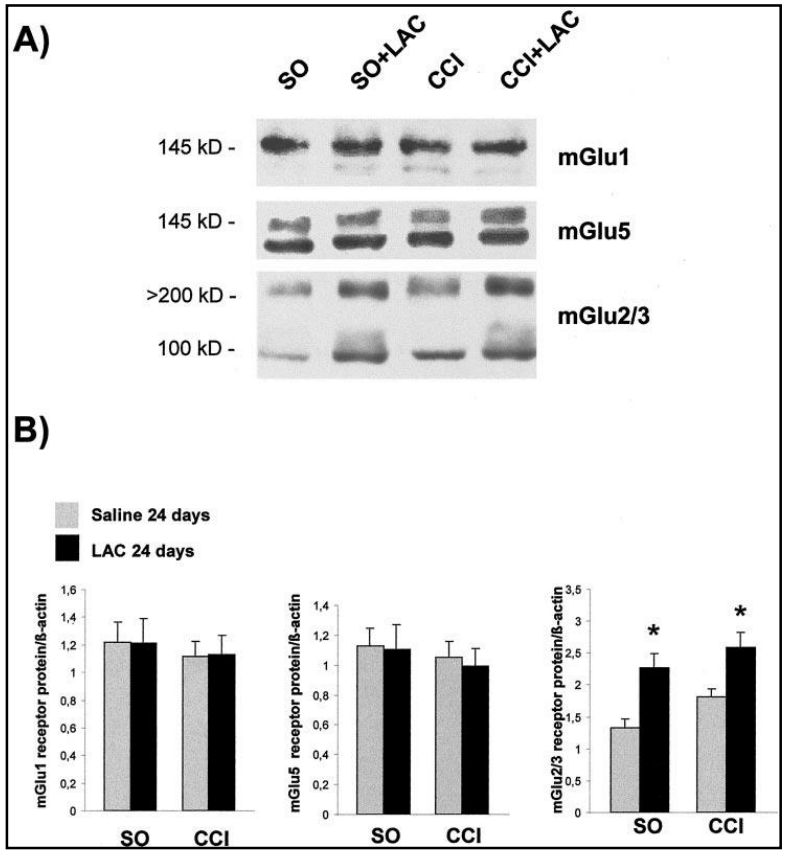


The analgesic activity of a 24-day treatment with LAC (100 mg/kg, s.c., once daily) against mechanical allodynia in CCI rats is prevented by a single injection of LY 341495 (1 mg/kg, i.p.). Animals were tested for mechanical allodynia 45 min after the acute injection of LY 341495 or saline.

Mol Pharmacol. 2002 May;61(5):989-96.

L-Acetylcarnitine induces analgesia by selectively up-regulating mGlu2 metabotropic glutamate receptors.

Chiechio S[1], Caricasole A, Barletta E, Storto M, Catania MV, Copani A, Vertechy M, Nicolai R, Calvani M, Melchiorri D, Nicoletti F.



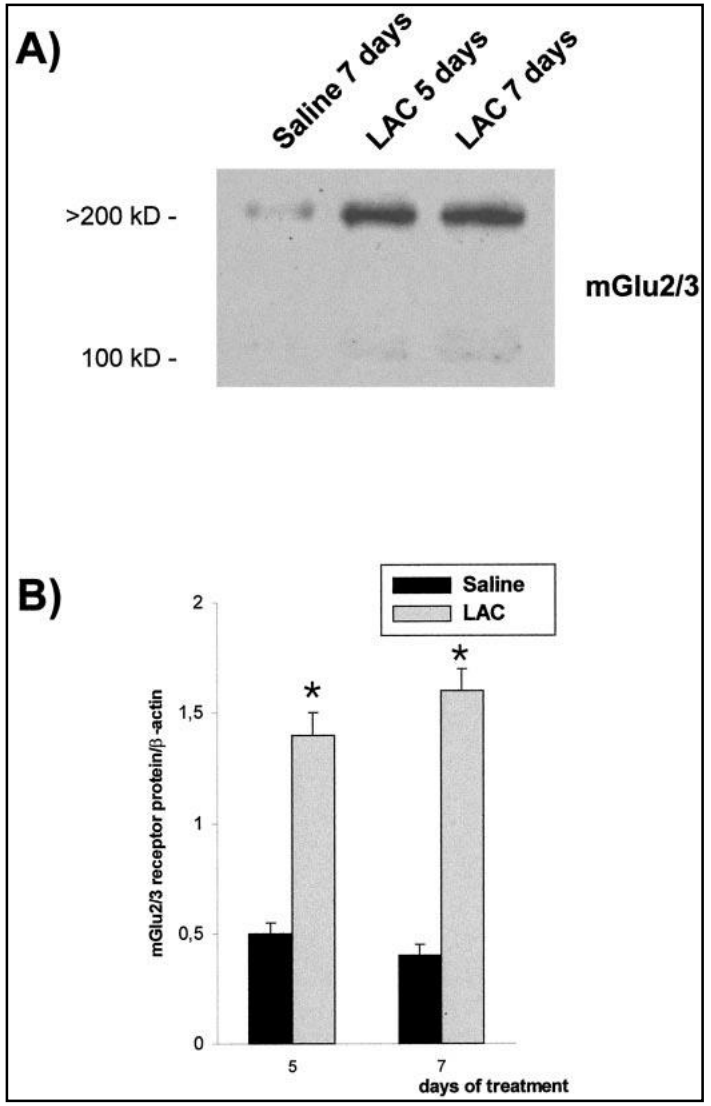
Expression of spinal mGlu2/3 receptors was markedly up-regulated by LAC treatment in both sham-operated and CCI rats.

A, Representative immunoblots of mGlu1, -5, and -2/3 receptors in the lumbar spinal cord of sham operated animals (SO), SO animals treated with LAC (100 mg/kg, s.c., once daily for 24 days), CCI animals, and CCI animals treated with LAC. Densitometric analysis of immunoblots is shown in B, where values (n6–8) were normalized by the expression of-actin. Note that LAC treatment selectively up-regulates the expression of mGlu2/3 receptors in both SO and CCI animals., p0.05 (Student's t test) versus values obtained in animals treated with saline for 24 days.

Mol Pharmacol. 2002 May;61(5):989-96.

L-Acetylcarnitine induces analgesia by selectively up-regulating mGlu2 metabotropic glutamate receptors.

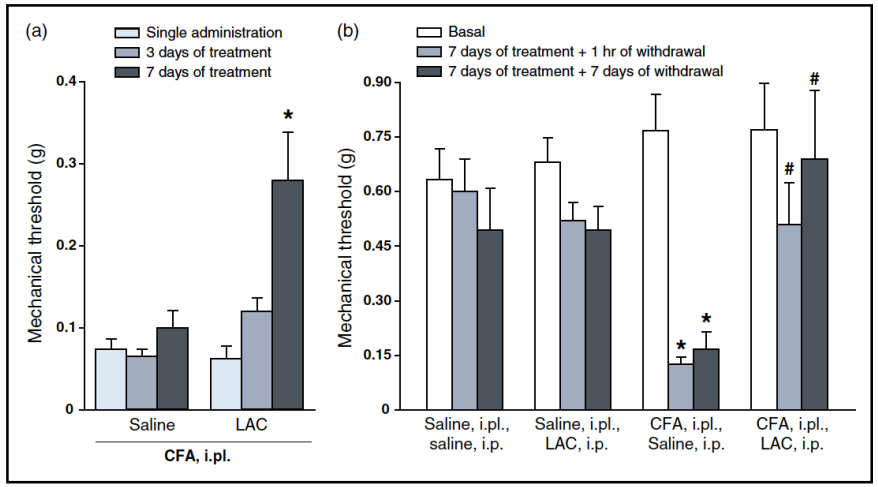
Chiechio S[1], Caricasole A, Barletta E, Storto M, Catania MV, Copani A, Vertechy M, Nicolai R, Calvani M, Melchiorri D, Nicoletti F.



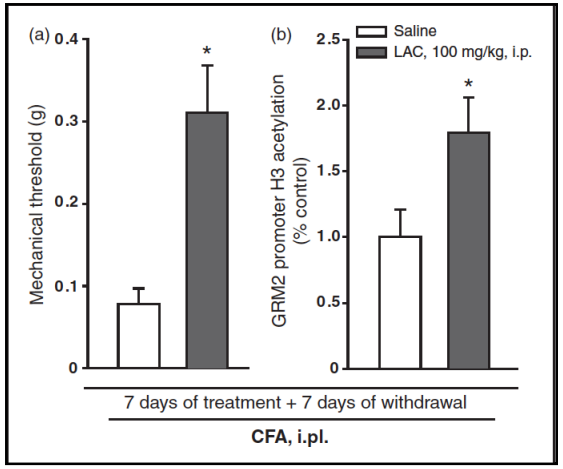
A, representative immunoblot of mGlu2/3 receptors in the dorsal root ganglia of intact rats treated with saline for 7 days or with LAC (100 mg/kg, i.p., twice daily) for 5 or 7 days. Densitometric analysis of immunoblots is shown in **B**, where values (n=4) were normalized by the expression of-actin., $p<0.05$ (Student's t test) versus the corresponding values obtained from animals treated with saline.

Mol Pain. 2017 Jan;13:1744806917697009. doi: 10.1177/1744806917697009.

Analgesia induced by the epigenetic drug, L-acetylcarnitine, outlasts the end of treatment in mouse models of chronic inflammatory and neuropathic pain.



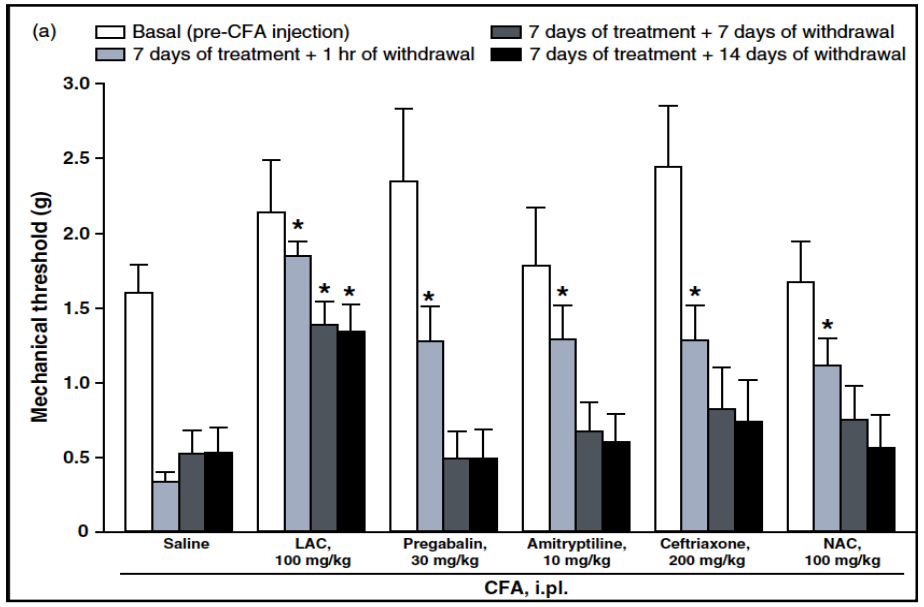
Effect of LAC on mechanical pain thresholds in the CFA mouse model of chronic inflammatory pain.



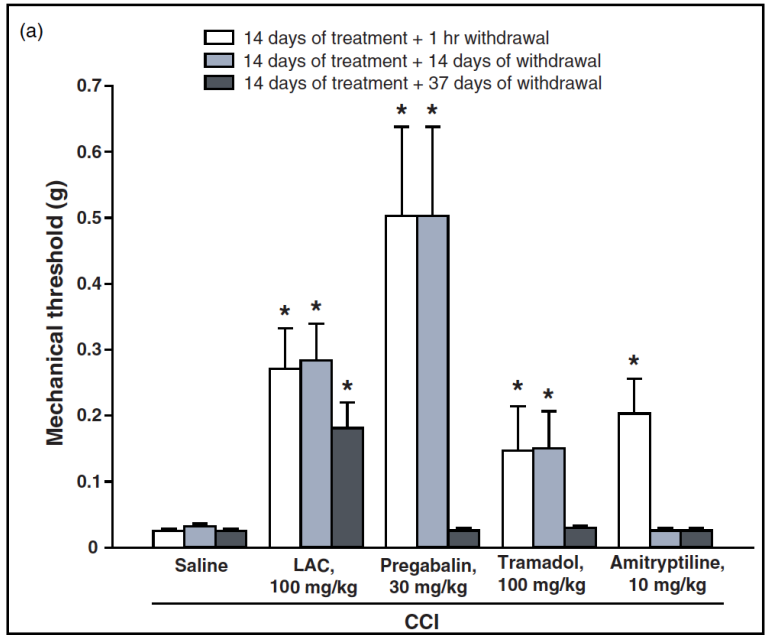
Increased levels of acetylated histone H3 bound to the Grm2 gene promoter in the dorsal root ganglia of mice with inflammatory pain treated with LAC

Mol Pain. 2017 Jan;13:1744806917697009. doi: 10.1177/1744806917697009.

Analgesia induced by the epigenetic drug, L-acetylcarnitine, outlasts the end of treatment in mouse models of chronic inflammatory and neuropathic pain.



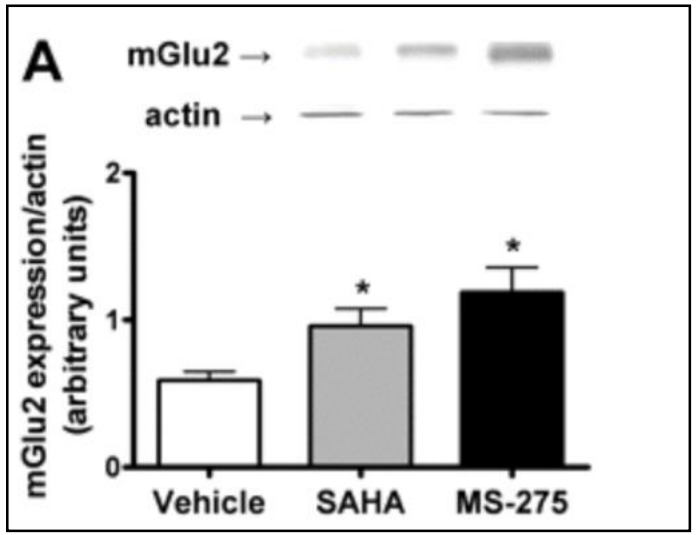
LAC has the unique property to induce a long-lasting analgesia in the CFA model of chronic inflammatory pain. Mice were injected i.p. with CFA and treated i.p. once a day for seven days with either saline, LAC (100 mg/kg), pregabalin (30 mg/kg), amitryptiline (10 mg/kg), pregabalin (30 mg/kg), ceftriaxone (200 mg/kg) or NAC (100 mg/kg). Pain thresholds measured under basal conditions, at the end of treatments, and then 7 and 14 days after drug withdrawal are shown in (a), where values are meansS.E.M. of 8 determinations.



LAC was less efficacious than pregabalin in enhancing mechanical pain thresholds in CCI mice, but its effect persisted after five weeks of drug withdrawal

Mol Pharmacol. 2009 May;75(5):1014-20. doi: 10.1124/mol.108.054346. Epub 2009 Mar 2.

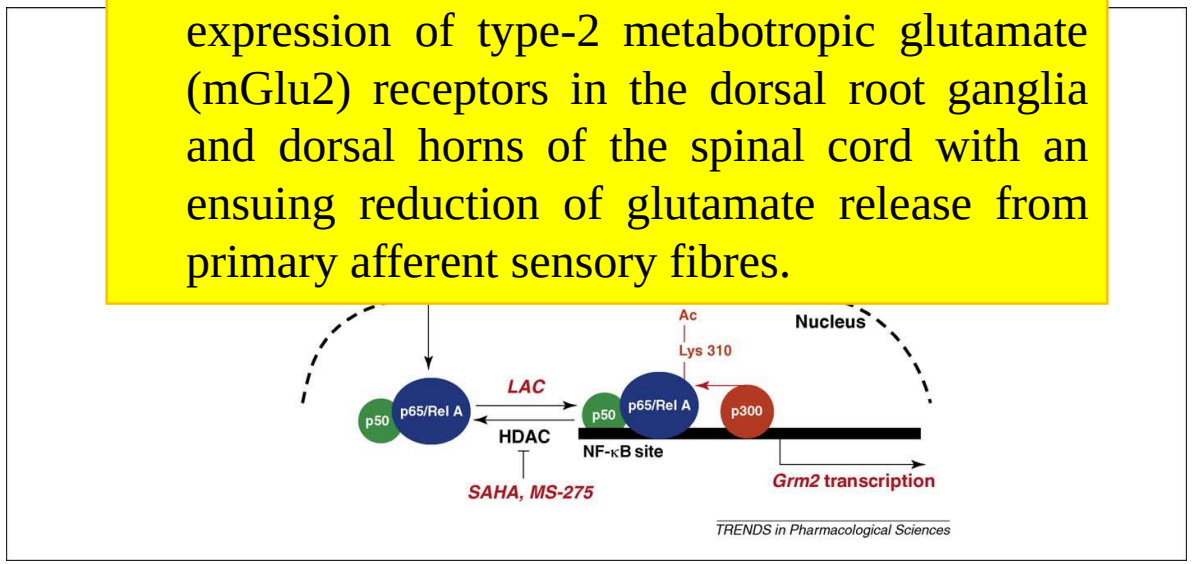
Epigenetic modulation of mGlu2 receptors by histone deacetylase inhibitors in the treatment of inflammatory pain.



HDAC inhibition produces analgesia by up-regulating mGlu2 receptor expression in the DRG, an effect that results from the amplification of NF-κB transcriptional activity

- LAC causes analgesia via an epigenetic mechanism mediated by acetylation of p65/RelA, a member of the NFkB family of transcription factors.

- Acetylation of p65/RelA leads to an enhanced expression of type-2 metabotropic glutamate (mGlu2) receptors in the dorsal root ganglia and dorsal horns of the spinal cord with an ensuing reduction of glutamate release from primary afferent sensory fibres.



Transcriptional regulation of the Grm2 gene by acetylation mechanisms.

Transcription of the Grm2 gene encoding the mGlu2 receptor is regulated by transcription factors of the NFkB family. These factors translocate into the cell nucleus when the inhibitory IkB subunit is phosphorylated and degraded (IKK = IkB kinase). Acetylation of Lys310 mediated by the coactivator, p300, is required for full transcriptional activity of p65/RelA.

LAC enhances Grm2 transcription by acting as a donor of acetyl groups to NFkB p65/RelA.

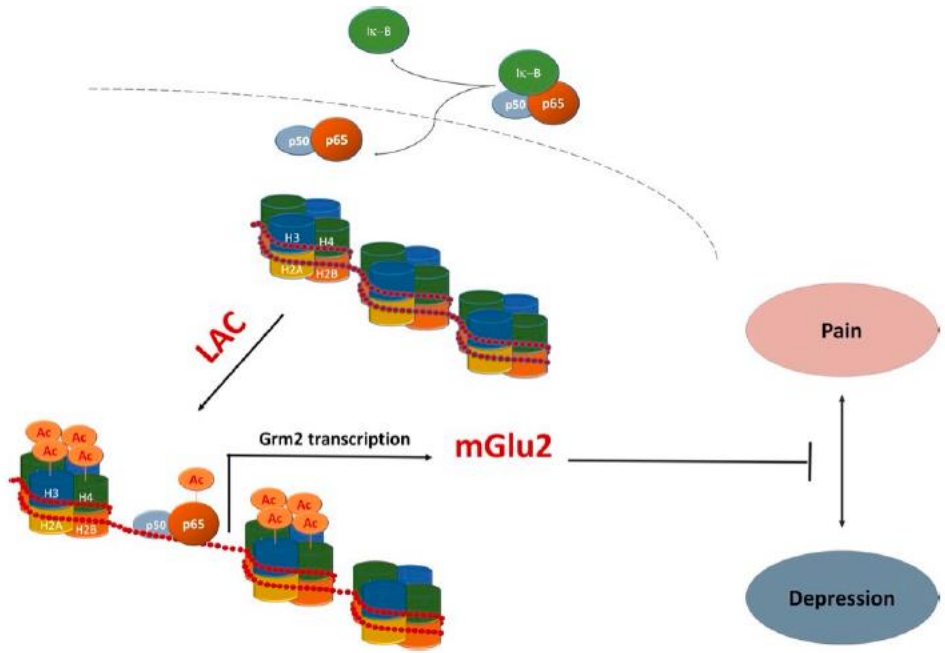
HDAC inhibitors, including SAHA and MS275, enhance Grm2 transcription by preventing deacetylation of p65/RelA

Int. J. Mol. Sci. **2018**, *19*, 11

Review

L-Acetylcarnitine: A Mechanistically Distinctive and Potentially Rapid-Acting Antidepressant Drug

Santina Chiechio [1], Pier Luigi Canonico [2] and Mariagrazia Grilli [3,*]



One potentially common mechanism underlying antidepressant and analgesic effects of LAC. LAC enhances *mGlu2* receptor (Grm2) gene transcription by acting as a donor of acetyl groups to NF-κB p65 and histones H3 and H4

Acetyl-L-carnitine deficiency in patients with major depressive disorder

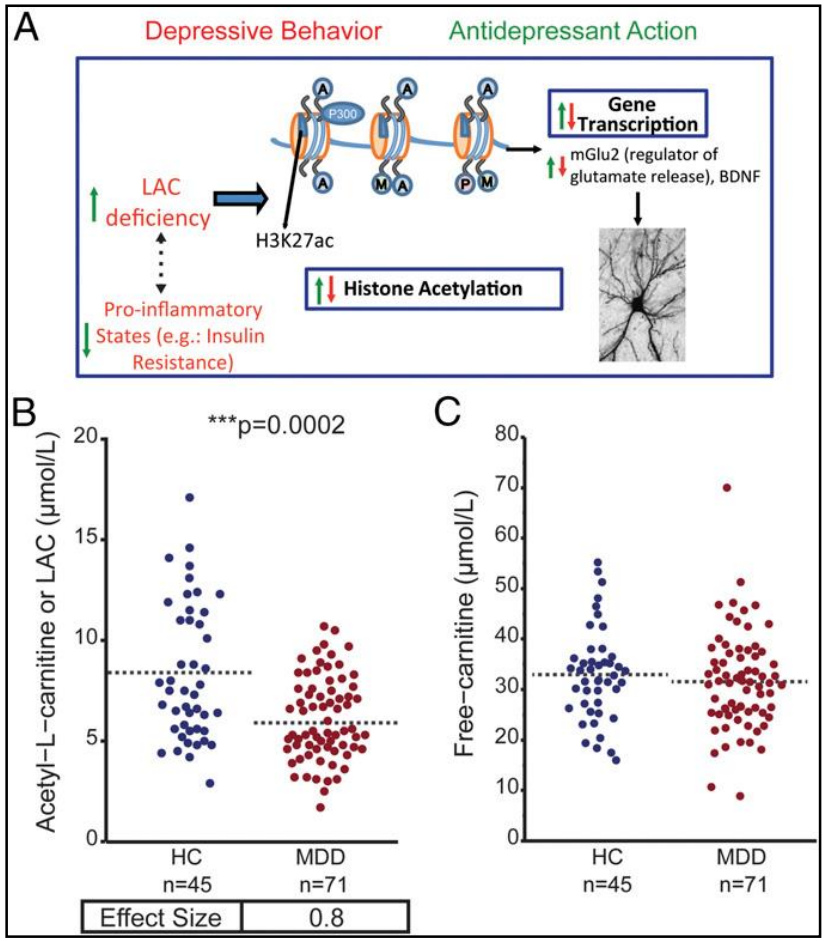
Carla Nasca, Benedetta Bigio, Francis S. Lee, Sarah P. Young, Marin M. Kautz, Ashly Albright, James Beasley, David S. Millington, Aleksander A. Mathé, James H. Kocsis, James W. Murrough, Bruce S. McEwen, and Natalie Rasgon

PNAS August 21, 2018 115 (34) 8627-8632; first published July 30, 2018

Decreased Acetyl-l-carnitine (LAC) Levels in patients with MDD compared with HC

(A) The endogenously produced molecule acetyl-l-carnitine(LAC) is critical for hippocampal function and several behavioral domains. **In rodents with depressive-like traits, LAC levels are markedly decreased** and accompanied by abnormal hippocampal glutamatergic function, decreased expression of the neurotrophic factor BDNF, and dendritic plasticity as well as by systemic inflammation, including insulin resistance. **LAC supplementation rescues those deficits and induces rapid and lasting epigenetic antidepressant-like effects via acetylation of histones.**

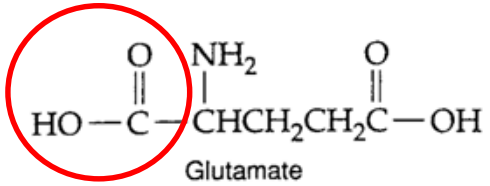
(B) (*B* and *C*) Plasma LAC (*B*) and free-carnitine (*C*) concentrations in HC and in patients with MDD in acute depressive episodes during study participation as assessed by ultraperformanceliquid chromatography–electrospray–tandem mass spectrometry(UPLC-MS/MS).



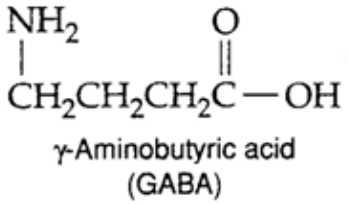
Somatic Pain

Epigenetic suppression of GAD65 expression mediates persistent pain

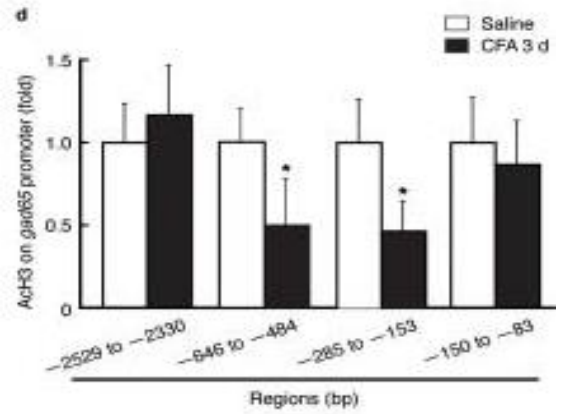
Persistent inflammatory and neuropathic pain epigenetically suppresses *gad65* activities through histone deacetylase (HDAC)-mediated histone hypoacetylation, resulting in impaired GABA synaptic inhibition

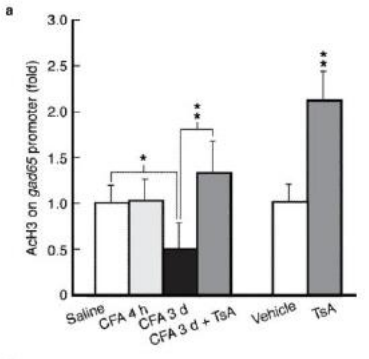


Glutamic Acid Decarboxylase (GAD)

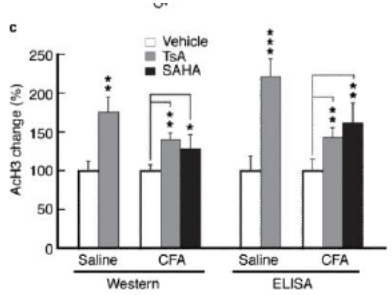


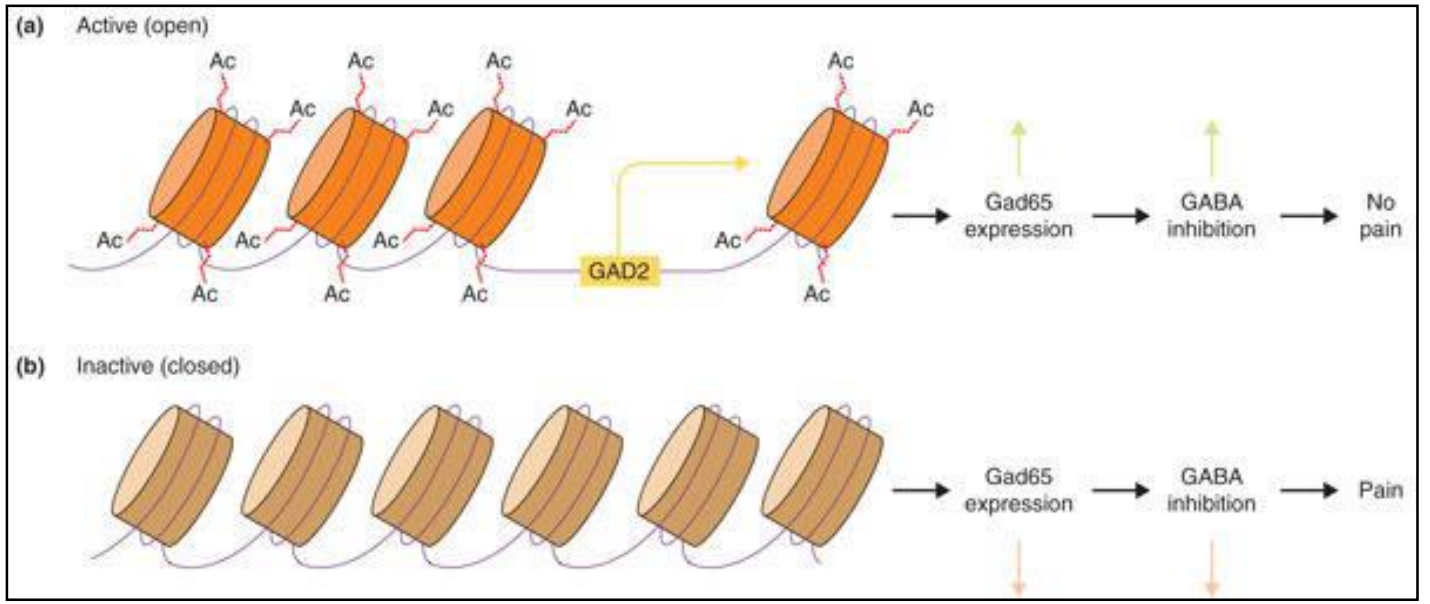
GAD65 is an antinociceptive gene.





HDAC inhibitors overwhelmingly increase gad65 activities, restore GABA synaptic function and relieve the sensitized pain behavior





Epigenetic regulation of gene expression in pain.

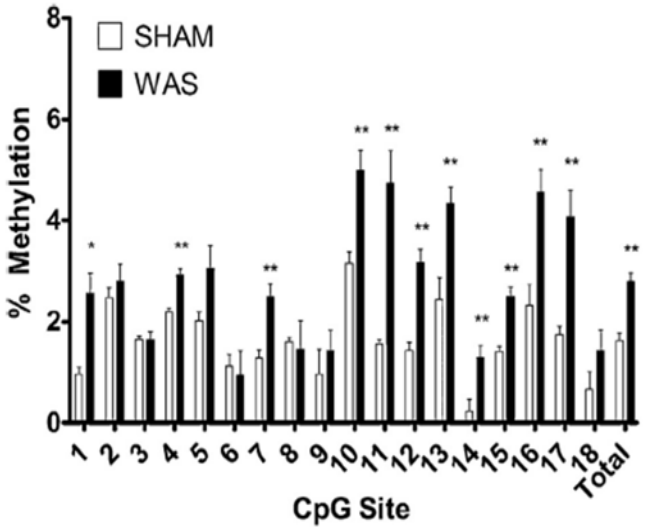
(a) In normal conditions hystonic tails are acetylated at GAD2 gene promoter in the nucleus raphe magnus.

(b) After treatment with Freund Adjuvant (CFA), GAD65 expression is supresses by the hypoacetylation of GAD2 promoter, thus leading to the loss of descending inhibiting nociceptive system (Crown, 2013).

Chronic visceral pain

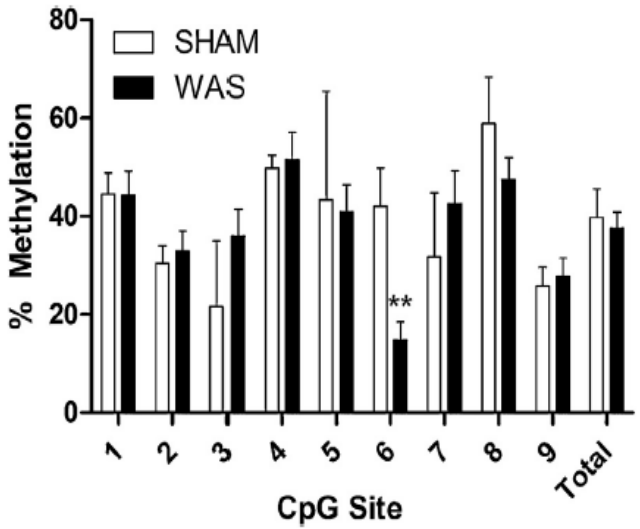
combination of hystone modifications and DNA methylation in pain neuraxis.

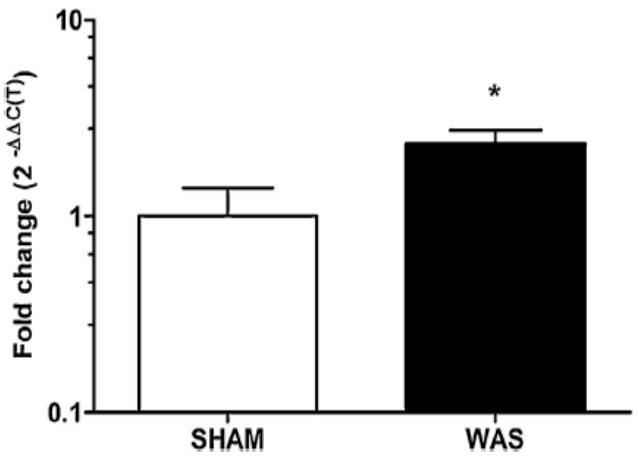
GR modulation



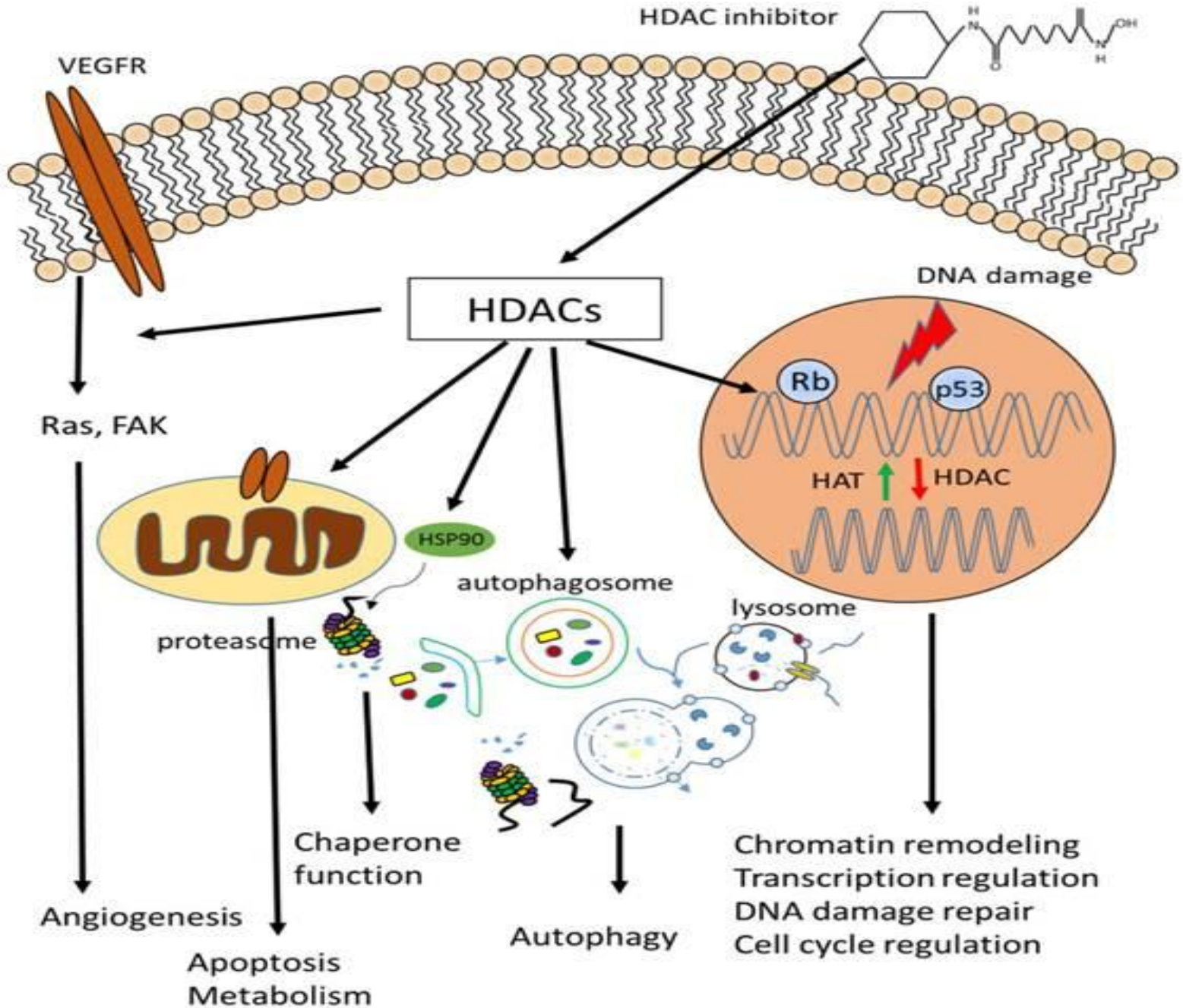
WAS=water avoidance stress

CRF modulation





Psychoneuroendocrinology.2013 Jun;38(6):898-906. doi: 10.1016/j.psyneuen.2012.09.016.


HDAC inhibitor
VEGFR
HDACs
DNA damage
Rb
p53
HAT
HDAC
Ras, FAK
HSP90
autophagosome
lysosome
proteasome
Chaperone function
Angiogenesis
Apoptosis
Metabolism
Autophagy
Chromatin remodeling
Transcription regulation
DNA damage repair
Cell cycle regulation

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Trends Neurosci. 2015 April ; 38(4): 237–246. doi:10.1016/j.tins.2015.02.001.

Epigenetic Mechanisms of Chronic Pain

Giannina Descalzi[1], **Daigo Ikegami**[2], **Toshikazu Ushijima**[3], **Eric Nestler**[1], **Venetia Zachariou**[1,*], and **Minoru Narita**[2,*]

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Published in final edited form as:
Epigenomics. 2015 April ; 7(2): 235–245. doi:10.2217/epi.14.75.

Epigenetic regulation of chronic pain

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Research Paper

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Epigenetics insights into chronic pain: DNA hypomethylation in fibromyalgia—a controlled pilot-study

Daniel Ciampi de Andrade[a,b], Mariana Maschietto[c], Ricardo Galhardoni[a,d,e,*], Gisele Gouveia[f], Thais Chile[f], Ana C. Victorino Krepischi[g], Camila S. Dale[a,h], André R. Brunoni[i,j], Daniella C. Parravano[a], Ana S. Cueva Moscoso[a], Irina Raicher[a,b], Helena H. S. Kaziyama[a], Manoel J. Teixeira[a,f], Helena P. Brentani[f]

Abstract

To evaluate changes in DNA methylation profiles in patients with fibromyalgia (FM) compared to matched healthy controls (HCs). All individuals underwent full clinical and neurophysiological assessment by cortical excitability (CE) parameters measured by transcranial magnetic stimulation. DNA from the peripheral blood of patients with FM (n = 24) and HC (n = 24) were assessed using the Illumina-HumanMethylation450 BeadChips. We identified 1610 differentially methylated positions (DMPs) in patients with FM displaying a nonrandom distribution in regions of the genome. Sixty-nine percent of DMP in FM were hypomethylated compared to HC. Differentially methylated positions were enriched in 5 genomic regions (1p34; 6p21; 10q26; 17q25; 19q13). The functional characterization of 960 genes related to DMPs revealed an enrichment for MAPK signaling pathway (n = 18 genes), regulation of actin cytoskeleton (n = 15 genes), and focal adhesion (n = 13 genes). A gene–gene interaction network enrichment analysis revealed the participation of DNA repair pathways, mitochondria-related processes, and synaptic signaling. Even though DNA was extracted from peripheral blood, this set of genes was enriched for disorders such as schizophrenia, mood disorders, bulimia, hyperphagia, and obesity. Remarkably, the hierarchical clusterization based on the methylation levels of the 1610 DMPs showed an association with neurophysiological measurements of CE in FM and HC. Fibromyalgia has a hypomethylation DNA pattern, which is enriched in genes implicated in stress response and DNA repair/free radical clearance. These changes occurred parallel to changes in CE parameters. New epigenetic insights into the pathophysiology of FM may provide the basis for the development of biomarkers of this disorder.

Keywords: Fibromyalgia, Chronic pain, Cortical excitability, DNA methylation, Epigenetics

MOLECULAR MEDICINE REPORTS 17: 2803-2810, 2018

Histone deacetylase 2 is involved in μ-opioid receptor suppression in the spinal dorsal horn in a rat model of chronic pancreatitis pain

YONG-HUI LIAO[1*], JIAN WANG[1*], YAN-YAN WEI[1], TING ZHANG[1], YONG ZHANG[1], ZHONG-FU ZUO[2], XIAO-YU TENG[1] and YUN-QING LI[1,3]

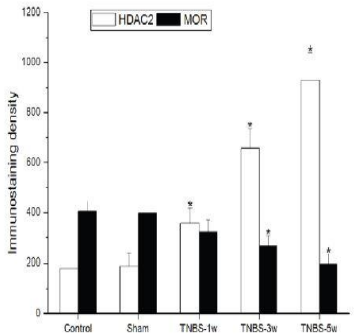

Figure 2. Immunostaining density of HDAC2 and MOR. Data are expressed as the mean ± standard error. *P<0.05 vs. control. HDAC2, histone deacetylase 2; MOR, μ-opiod receptor; TNBS, trinitrobenzene sulfonic acid; w, week.

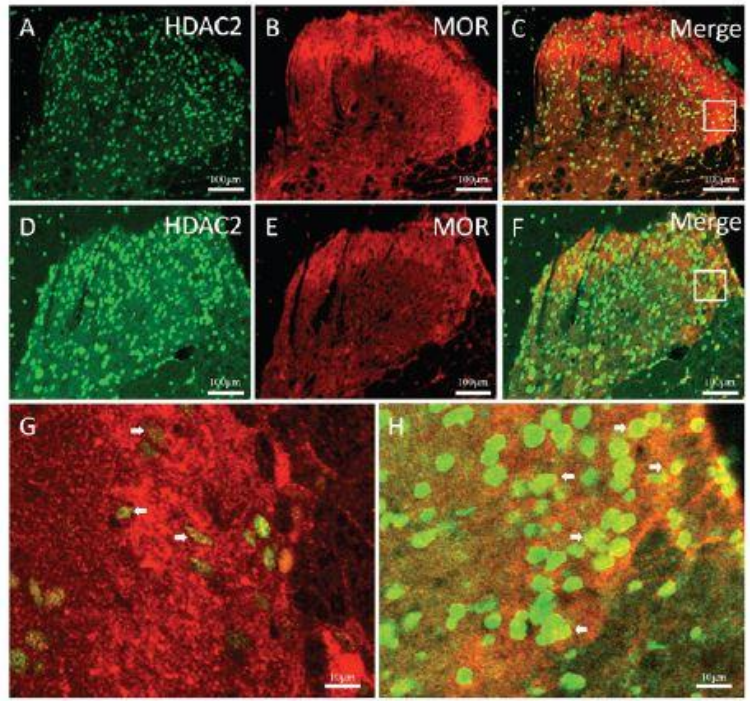

Figure 1. Immunofluorescent double staining for HDAC2 and MOR in the thoracic spinal dorsal horn of CP-induced rats. Immunoreactivities of (A) HDAC2 (green), (B) MOR (red) and (C) merge in the control group. Immunoreactivities of (D) HDAC2, (E) MOR and (F) merge in the CP group. (G) and (H) represent magnified images of the rectangles indicated in the above panels. White arrows indicate areas of merged overlap of HDAC2 and MOR. HDAC2, histone deacetylase 2; MOR, μ-opiod receptor; CP, chronic pancreatitis.

Pharmacoepigenetics of the role of DNA methylation in μ-opioid receptor expression in different human brain regions

Aim: Exposure to opioids has been associated with epigenetic effects. Studies in rodents suggested a role of varying degrees of DNA methylation in the differential regulation of μ-opioid receptor expression across the brain. **Methods:** In a translational investigation, using tissue acquired postmortem from 21 brain regions of former opiate addicts, representing a human cohort with chronic opioid exposure, μ-opioid receptor expression was analyzed at the level of DNA methylation, mRNA and protein. **Results & conclusion:** While high or low μ-opioid receptor expression significantly correlated with local *OPRM1* mRNA levels, there was no corresponding association with *OPRM1* methylation status. Additional experiments in human cell lines showed that changes in DNA methylation associated with changes in μ-opioid expression were an order of magnitude greater than differences in brain. Hence, different degrees of DNA methylation associated with chronic opioid exposure are unlikely to exert a major role in the region-specificity of μ-opioid receptor expression in the human brain.

Claudia Knothe[1], Bruno G Oertel[2], Alfred Ultsch[3], Mattias Kettner[5], Peter Harald Schmidt[4], Cora Wunder[5], Stefan W Toennes[5], Gerd Geisslinger[1,2] & Jörn Lötsch*[,1,2]

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Demethylation regulation of BDNF gene expression in dorsal root ganglion neurons is implicated in opioid-induced pain hypersensitivity in rats

Yu-Chieh Chao [a], Fang Xie [a], Xueyang Li [a], Ruijuan Guo [b], Ning Yang [a,c], Chen Zhang [a]

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 291, NO. 16, pp. 8475–8485, April 15, 2016

Nerve Injury Diminishes Opioid Analgesia through Lysine Methyltransferase-mediated Transcriptional Repression of μ-Opioid Receptors in Primary Sensory Neurons*

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Nat Rev Neurol. 2017 Jul;13(7):434-447. doi: 10.1038/nrneurol.2017.68. Epub 2017 May 26.

Drugging the pain epigenome.

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Author information

Abstract

More than 20% of adults worldwide experience different types of chronic pain, which are frequently associated with several comorbidities and a decrease in quality of life. Several approved painkillers are available, but current analgesics are often hampered by insufficient efficacy and/or severe adverse effects. Consequently, novel strategies for safe, highly efficacious treatments are highly desirable, particularly for chronic pain. Epigenetic mechanisms such as DNA methylation, histone modifications and microRNAs (miRNAs) strongly affect the regulation of gene expression, potentially for long periods over years or even generations, and have been associated with pathophysiological pain. Several studies, mostly in animals, revealed that inhibitors of DNA methylation, activators and inhibitors of histone modification and modulators of miRNAs reverse a number of pathological changes in the pain epigenome, which are associated with altered expression of pain-relevant genes. This epigenetic modulation might then reduce the nociceptive response and provide novel therapeutic options for analgesic therapy of chronic pain states. However, a number of challenges, such as nonspecific effects and poor delivery to target cells and tissues, hinder the rapid development of such analgesics. In this Review, we critically summarize data on epigenetics and pain, focusing on challenges in clinical development as well as possible new approaches to the drug modulation of the pain epigenome.

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Chronic opioid use is associated with increased DNA methylation correlating with increased clinical pain

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Abstract

Summary: Chronic opioid exposure is associated with *OPRM1* and global DNA hypermethylation. Global DNA methylation correlates with chronic pain in opioid-treated but not non-opioid-treated patients.

Abstract: Environmentally caused changes in chromosomes that do not alter the DNA sequence but cause phenotypic changes by altering gene transcription are summarized as epigenetics. A major epigenetic mechanism is methylation or demethylation at CpG-rich DNA islands. DNA methylation triggered by drugs has largely unexplored therapeutic consequences. Here we report increased methylation at a CpG rich island in the *OPRM1* gene coding for μ-opioid receptors and at a global methylation site (LINE-1) in leukocytes of methadone-substituted former opiate addicts compared with matched healthy controls. Higher DNA methylation associated with chronic opioid exposure was reproduced in an independent cohort of opioid-treated as compared to non-opioid-treated pain patients. This suggests that opioids may stimulate DNA methylation. The *OPRM1* methylation had no immediate effect on μ-opioid receptor transcription and was not associated with opioid dosing requirements. However, the global DNA methylation at LINE-1 was significantly correlated with increased chronic pain. This suggests inhibitory effects on the transcription of still unspecified nocifensive gene products. It further implies that opioids may be causally associated with increased genome-wide DNA methylation, although currently there is no direct evidence of this. This has phenotypic consequences for pain and may provide a new, epigenetics-associated mechanism of opioid-induced hyperalgesia. The results indicate a potential influence of opioid analgesics on the patients' epigenome. They emphasize the need for reliable and cost-effective screening tools and may imply that high-throughput screening for lead compounds in artificial expression systems may not provide the best tools for identifying new pain medications.

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ORIGINAL RESEARCH

DNMT3a methylation in neuropathic pain

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Background: Mu opioid receptor (MOR) plays a crucial role in mediating analgesic effects of opioids and is closely associated with the pathologies of neuropathic pain. Previous studies have reported that peripheral nerve injury downregulates MOR expression, but the epigenetic mechanisms remain unknown.

Objective: Therefore, we investigated DNA methyltransferase3a (DNMT3a) expression or methylation changes within MOR promoter in the spinal cord in a neuropathic pain induced by a chronic constriction injury (CCI) mouse model and further determined whether these injury-associated changes are reversible by pharmacological interventions.

Methods: A CCI mouse model was established and tissue specimens of lumbar spinal cords were collected. The nociception threshold was evaluated by a Model Heated 400 Base. DNMT3a and MOR mRNA and protein level were detected by real-time-polymerase chain reaction and Western blot, respectively. Methylation of *DNMT3a* gene was measured by methylation-specific PCR.

Results: Our data showed that chronic nerve injury led to a significant upregulation of DNMT3a expression that was associated with increased methylation of MOR gene promoter and decreased MOR protein expression in the spinal cord. Inhibition of DNMT3a catalytic activity with DNMT inhibitor RG108 significantly blocked the increase in methylation of the MOR promoter, and then upregulated MOR expression and attenuated thermal hyperalgesia in neuropathic pain mice.

Conclusion: This study demonstrates that an increase of DNMT3a expression and MOR methylation epigenetically play an important role in neuropathic pain. Targeting DNMT3a to the promoter of MOR gene by DNMT inhibitor may be a promising approach to the development of new neuropathic pain therapy.

Opioid Receptors

Both demethylating agents and histone deacetylase inhibitors increase expression of the μ-opioid receptor(137), indicating that the endogenous opioid system is under significant epigenetic control. Consistent with these laboratory findings, increased CpG methylation has been noted in the promoter regions of the μ-opioid receptors of heroin users, consistent with receptor downregulation(76). Likewise, DNA methylation of the proenkephalin gene promoter inhibits transcription and gene expression of this opioid peptide(63).

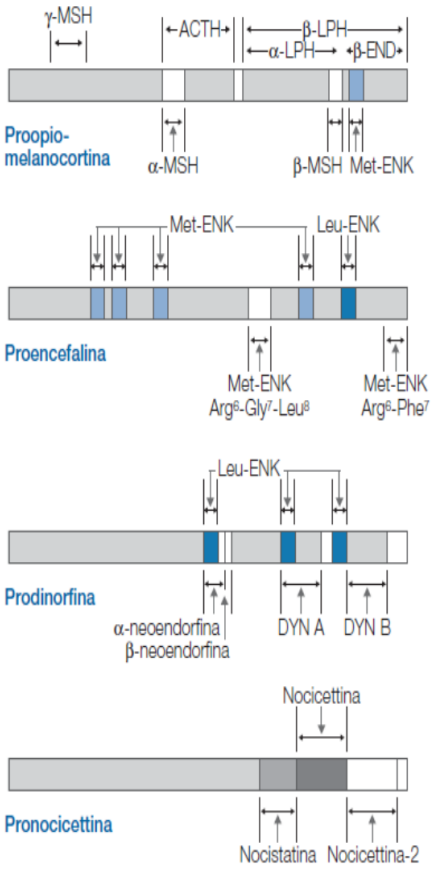
Beyond the direct role of methylation in the regulation of opioid peptide expression, spinal opioid receptor activity also appears to be partially modulated by central glucocorticoid receptors(138). This association is of particular importance given the synergy between the increased central expression of GR following peripheral nerve injury(139) and direct epigenetic manipulation of the endogenous opioid system(63, 137). The interaction between modifications of the GR and the opioid receptor demonstrates the complex role that epigenetic alterations play in controlling the inflammatory and pain-modulating pathways.

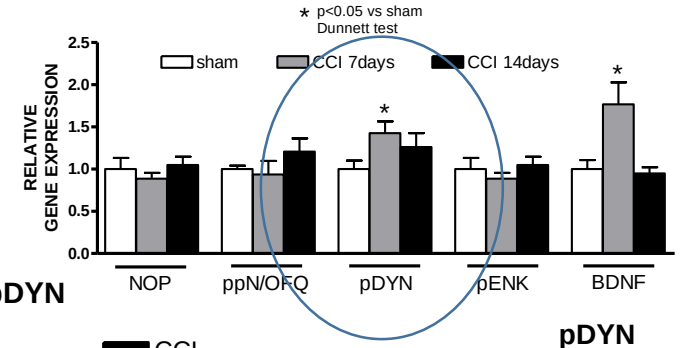
Group	Compound	HDAC target[1]	Current state
Hydroxamic acid	Vorinostat (SAHA, Zolinza)	class I, II, IV	FDA approved
	Panobinostat (LBH589)	class I, II, IV	phase III CT
	Belinostat (PXD101)	class I, II, IV	phase II CT
	Abexinostat (PCI24781)	class I, II	phase II CT
	Resminostat (RAS2410)	class I, II	phase II CT
	Givinostat (ITF2357)	class I, II	phase II CT
	Dacinostat (LAQ824, NVP-LAQ824)	class I, II	phase I CT
	Pracinostat (SB939)	class I, II	phase II CT
Cyclic tetrapeptide	Romidepsin (Depsipeptide, FK228)	HDAC1, 2	FDA approved
	Apicidin	HDAC2, 3	Phase II CT
	Trapoxin A	HDAC1, 4, 11	ND[2]
Benzamide	Mocetinostat (MGCD0103)	HDAC1, 2, 11	phase II CT
	Entinostat (MS-275, SNDX-275)	HDAC1, 9, 11	phase II CT
	Rocilinostat (ACY-1215)	HDAC6	phase II CT
Aliphatic acid	Valproic acid (VPA)	class I	phase III CT
	Pivanex (AN-9)	ND	phase II CT
	Butyrate	class I, IIa	Phase II CT
Electrophilic ketone	Trifluorometchylketone	ND	ND

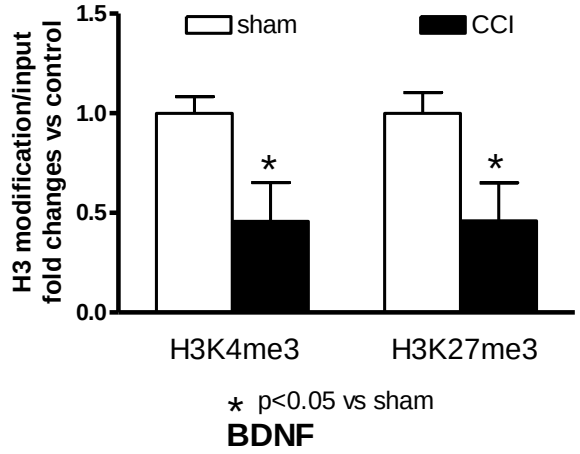
HDAC inhibitors currently under clinical investigation.

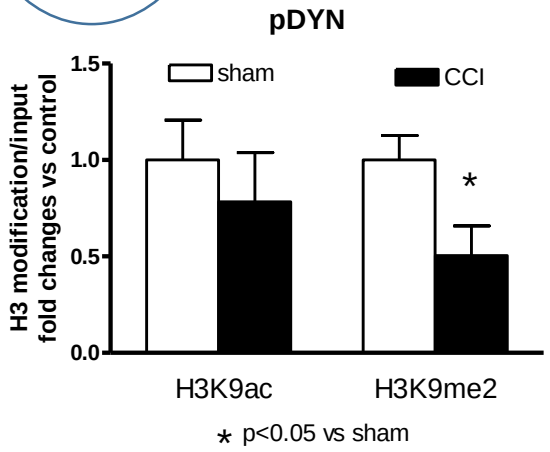
most inhibitors are at different stages of clinical trials, **SAHA and Depsipeptide have been approved by FDA for cancer chemotherapeutic intervention.**

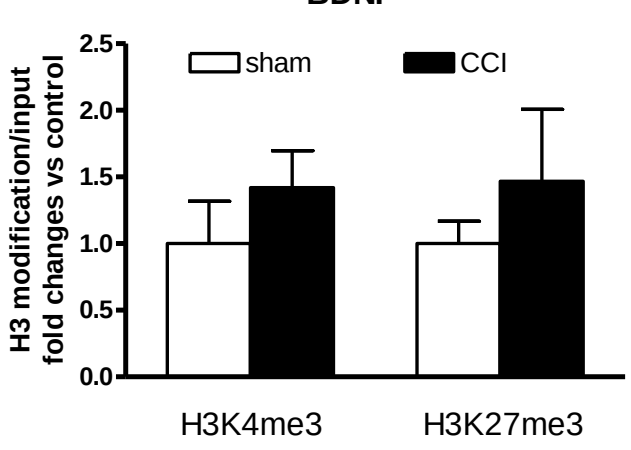
HISTONE MODIFICATIONS In CCI model of neuropathic pain

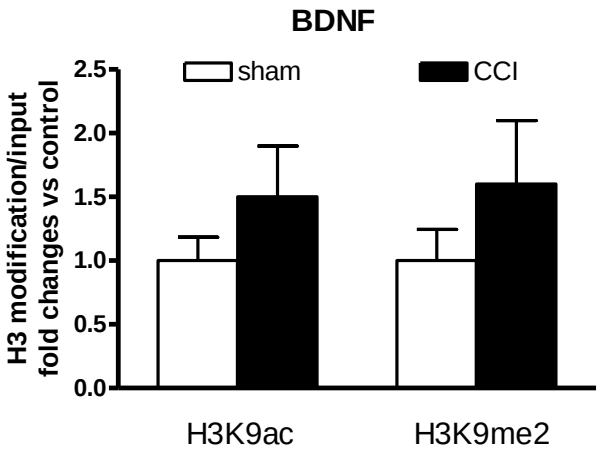












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….E studi clinici in corso….di metilazione del OPRM1 nel dolore cronico postoperatorio

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Research papers

Chronic opioid use is associated with increased DNA methylation correlating with increased clinical pain

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frontiers in Pharmacology

ORIGINAL RESEARCH
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An Exploratory Pilot Study of Changes in Global DNA Methylation in Patients Undergoing Major Breast Surgery Under Opioid-Based General Anesthesia

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Alessio Squassina, University of Cagliari, Italy

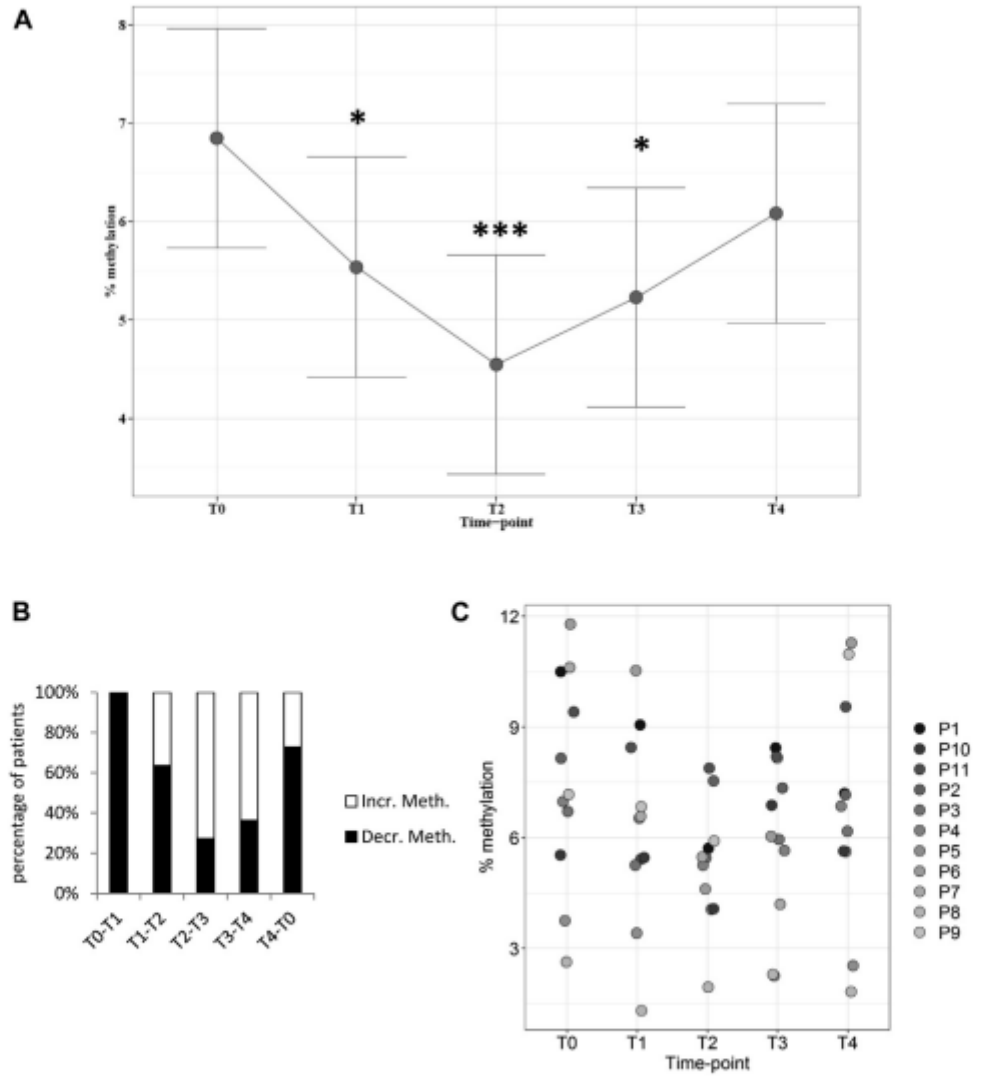


FIGURE 1 | Global DNA methylation levels in patients at different time-points. **(A)**: Plot of the least square predicted means with 95% confidence intervals. The predicted least square means were calculated using a 1-way repeated measures mixed model. *$p < 0.05$; ***$p < 0.001$ in planned comparisons with T0 levels. **(B)**: variation in methylation levels between time-points. The percentage of patients showing increased (Incr. Meth.) or decreased (Decr. Meth.) methylation levels with respect to the previous time-point is shown. **(C)**: DNA methylation levels in each patient at every time-point. $n = 11$ patients repeatedly assessed at 5 time-points.

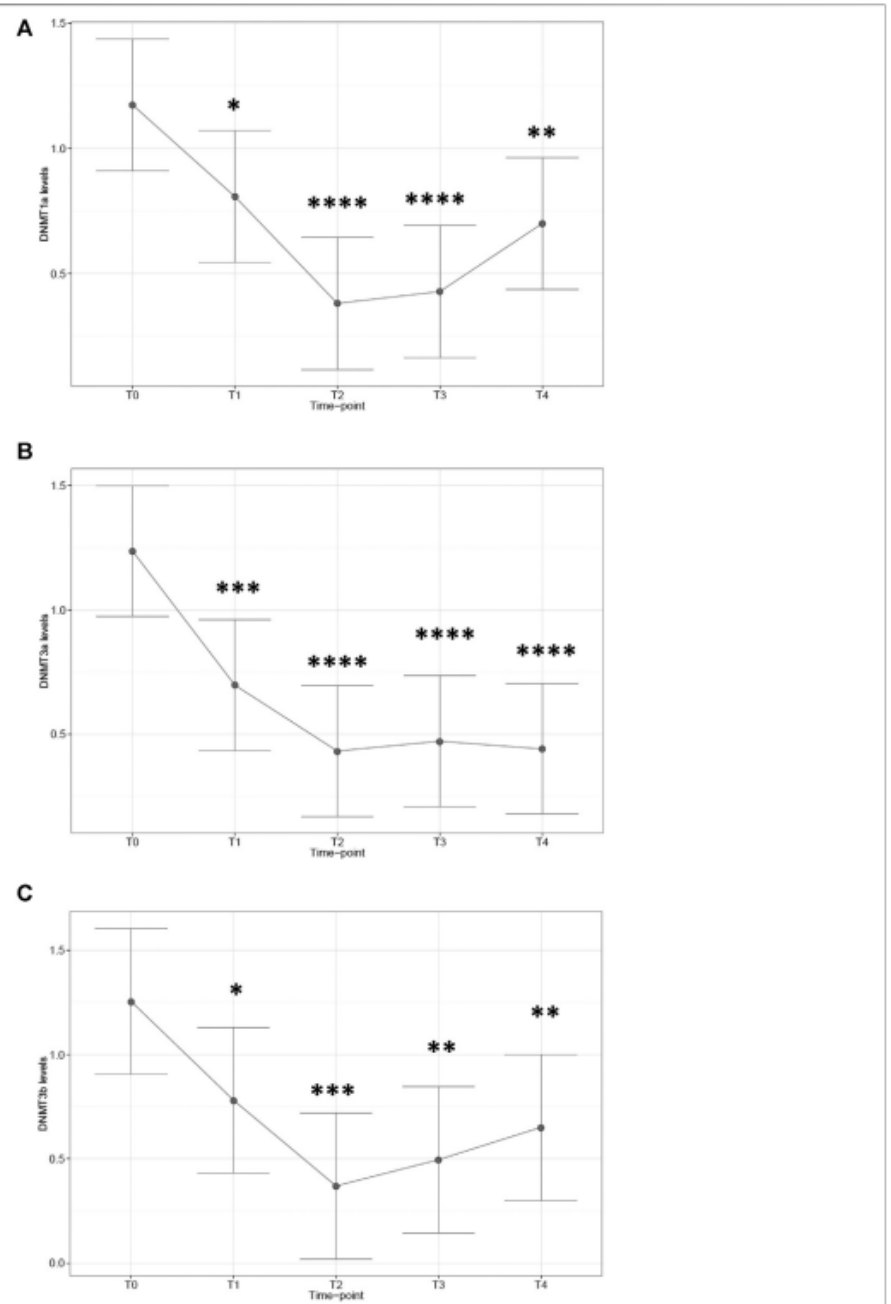
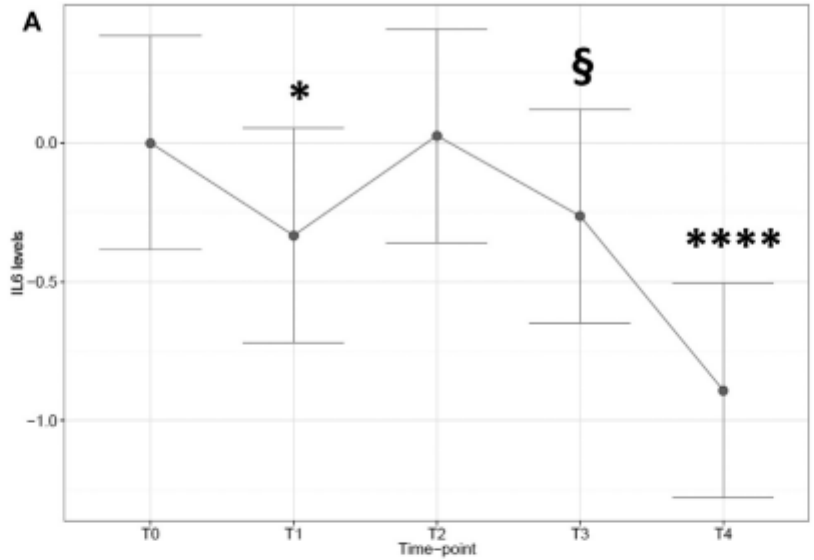


FIGURE 2 | mRNA expression of DNA methyltransferase isoforms in patients at different time-points. Plot of the least square predicted means with 95% confidence intervals. The predicted least square means were calculated using a 1-way repeated measures mixed model. **(A)**: DNMT1a; **(B)**: DNMT3a; **(C)**: DNMT3b. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$ in planned comparisons with T0 levels. $n = 11$ patients repeatedly assessed at 5 time-points.



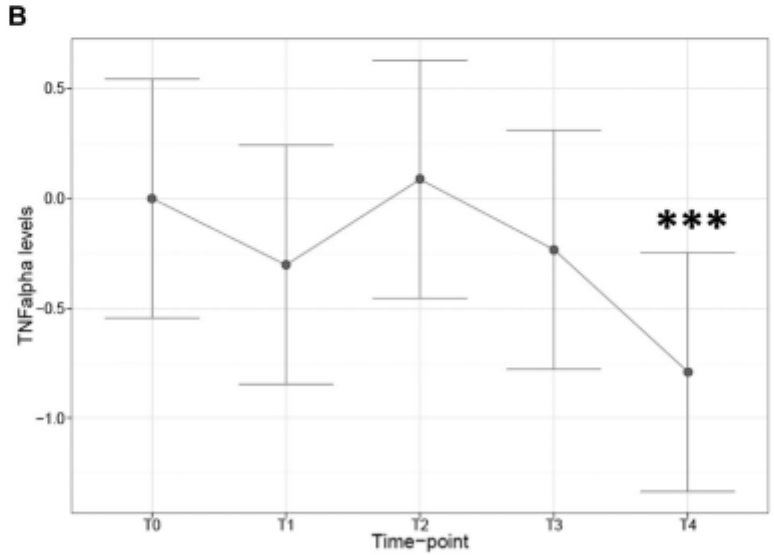
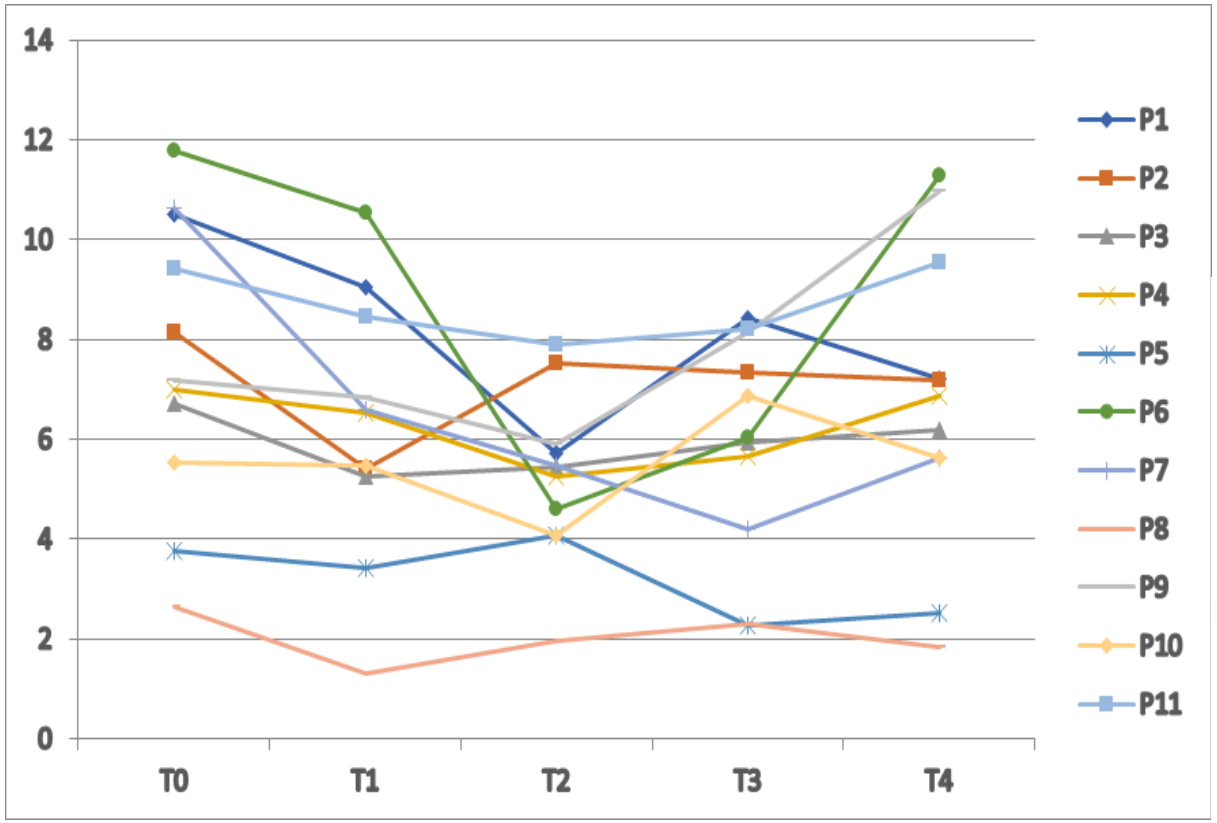


FIGURE 3 | Cytokine mRNA expression in patients at different time-points. Plot of the least square predicted means with 95% confidence intervals. The predicted least square means were calculated using a 1-way repeated measures mixed model. **(A)**: IL6; **(B)**: TNFα. Ordinate axis is displayed on the Log10 scale. *$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$; §$0.05 < p < 0.1$ in planned comparisons with T0 levels. $n = 11$ patients repeatedly assessed at 5 time-points.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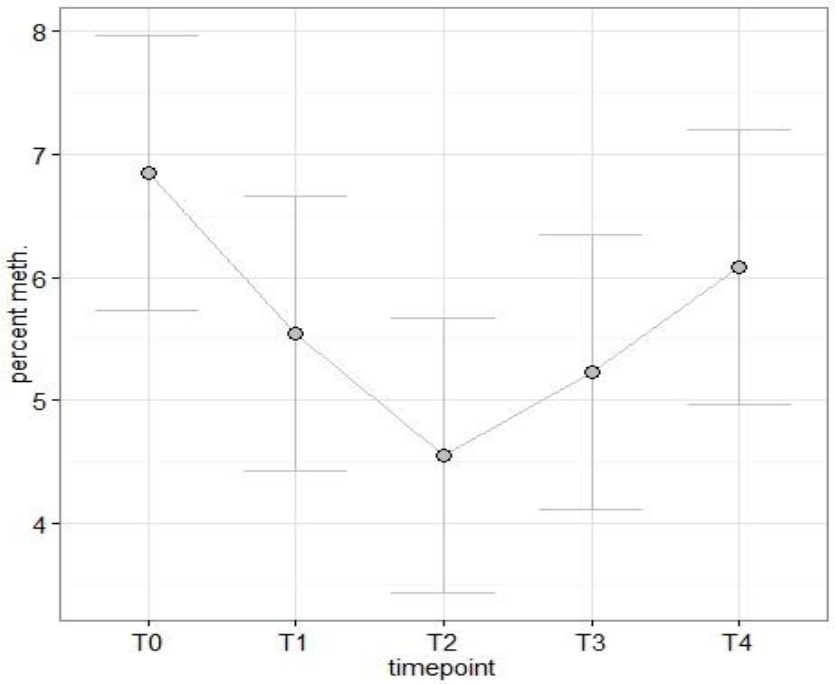
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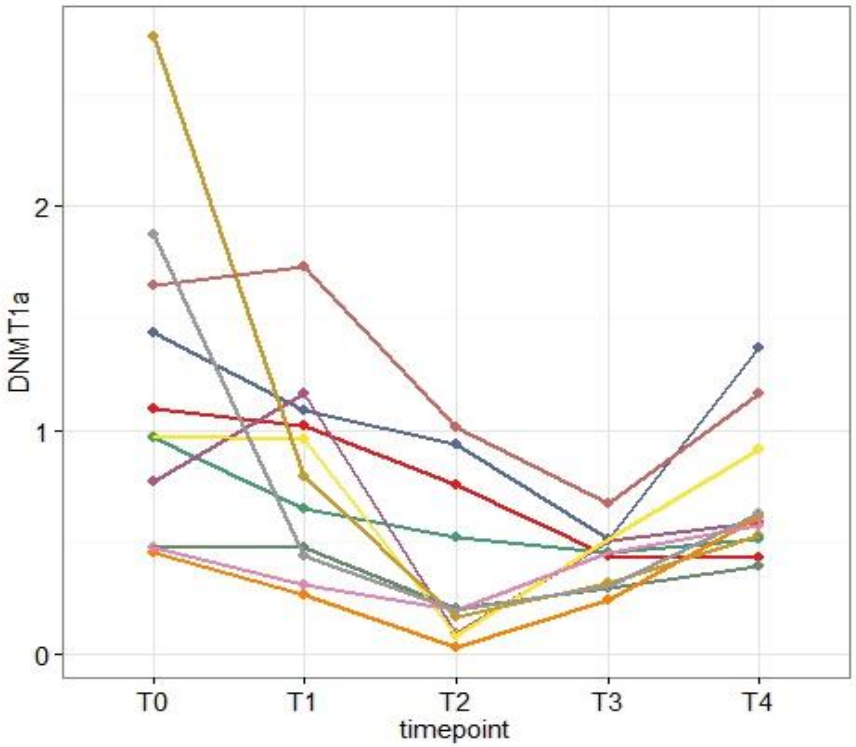
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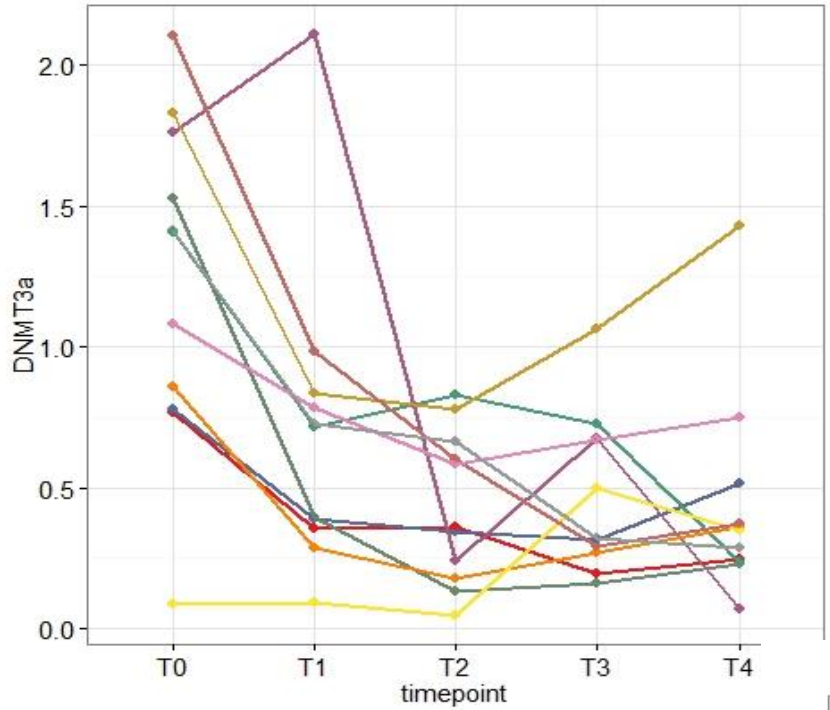
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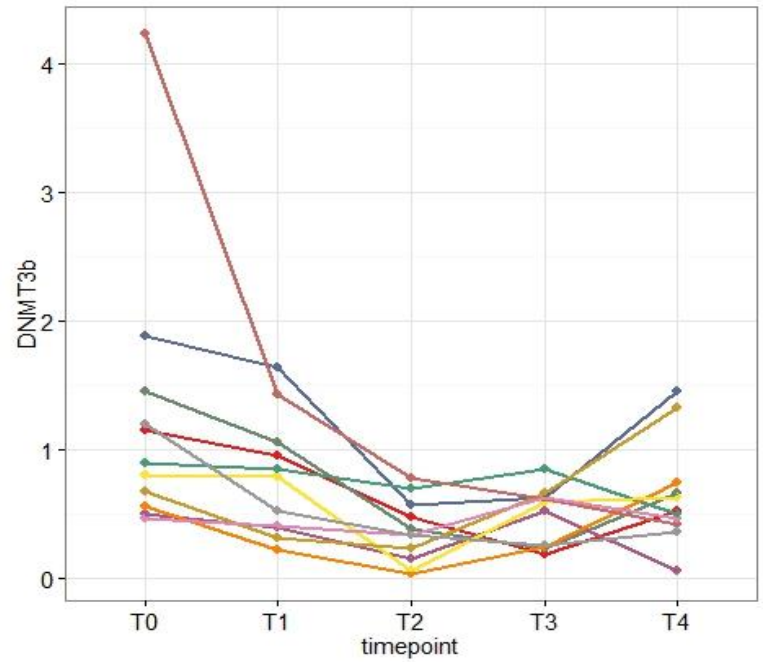
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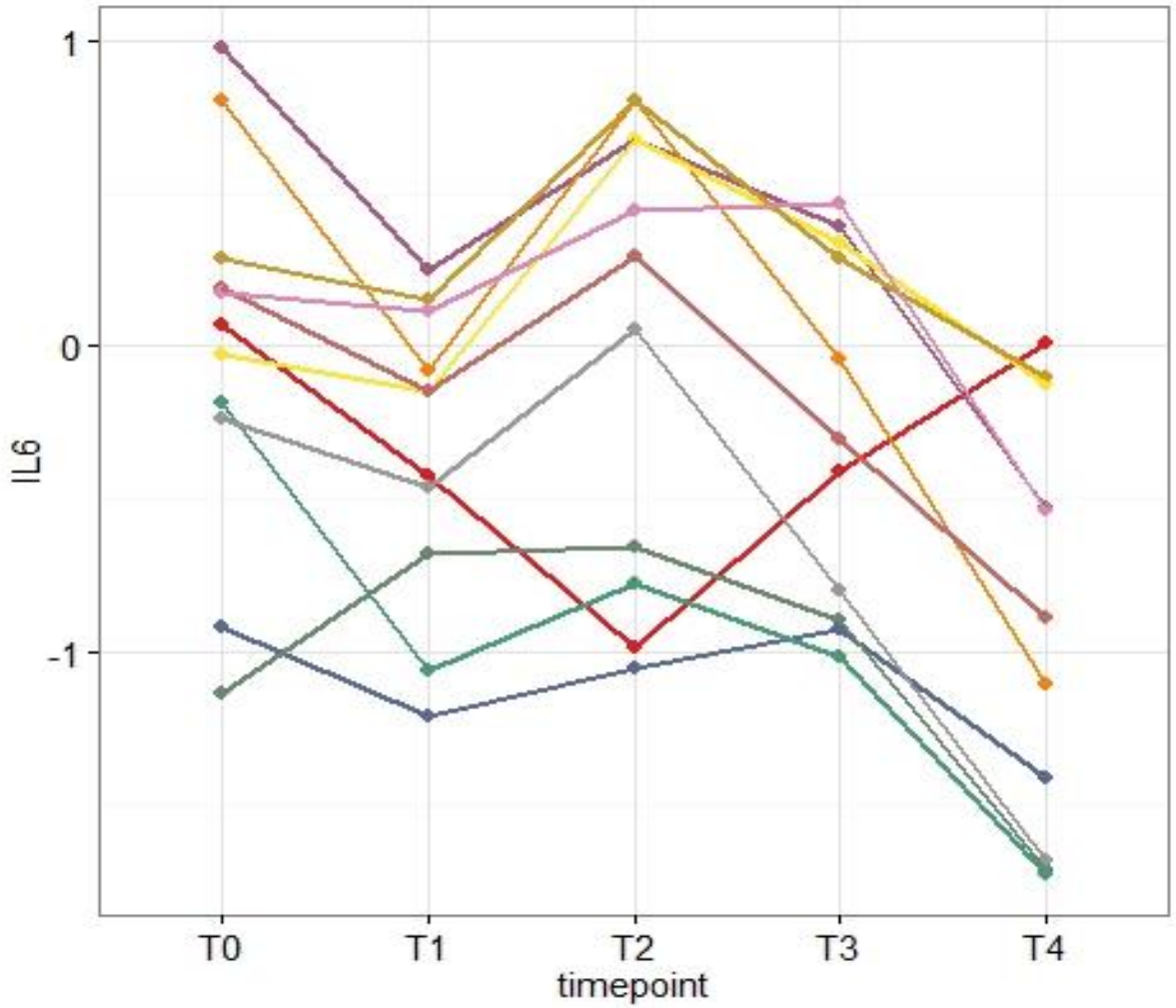
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Crow *et al. Genome Medicine* 2013, 5:12
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Genome Medicine

REVIEW

Genes and epigenetic processes as prospective pain targets

Megan [illegible]* Franziska Denk and Stephen B McMahon*

Perspective of development of pharmacological intervention on new targets for the prevention of neuropathic pain

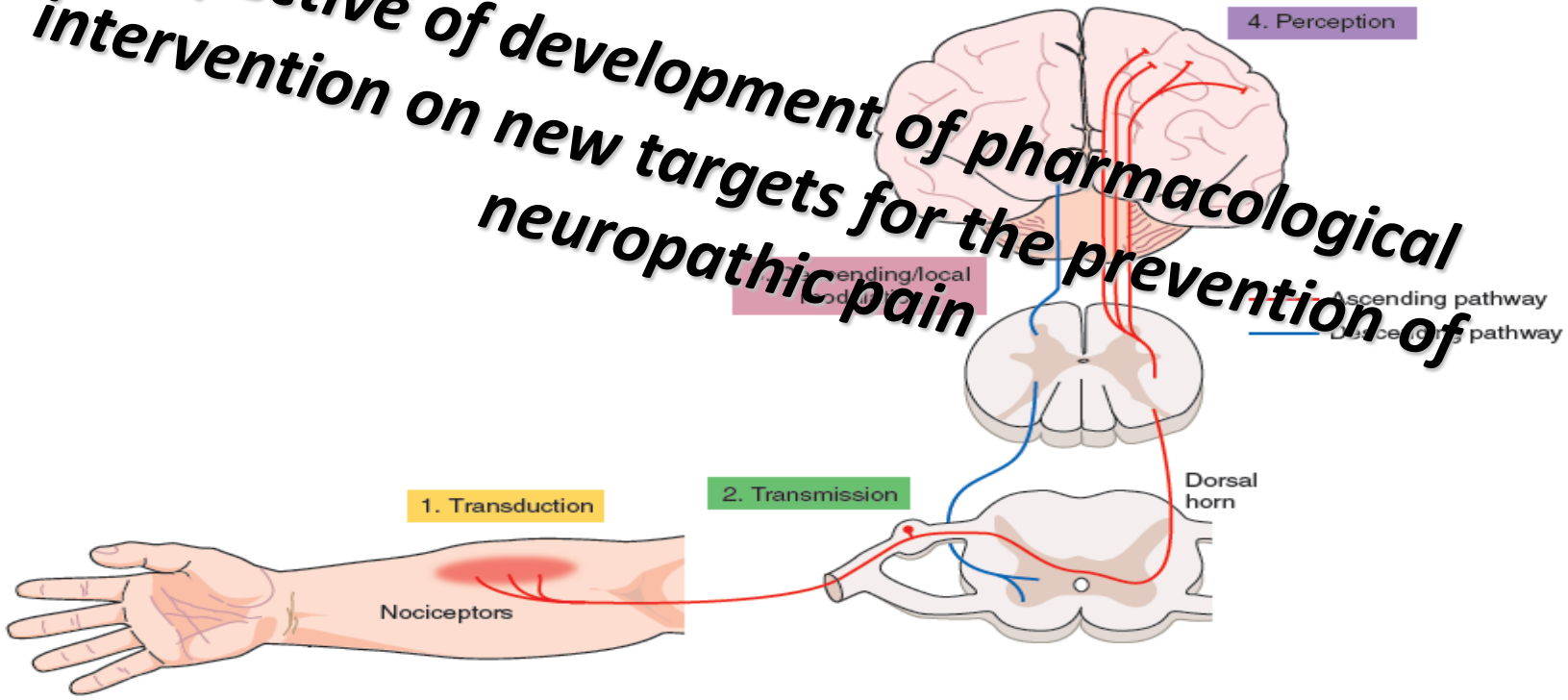
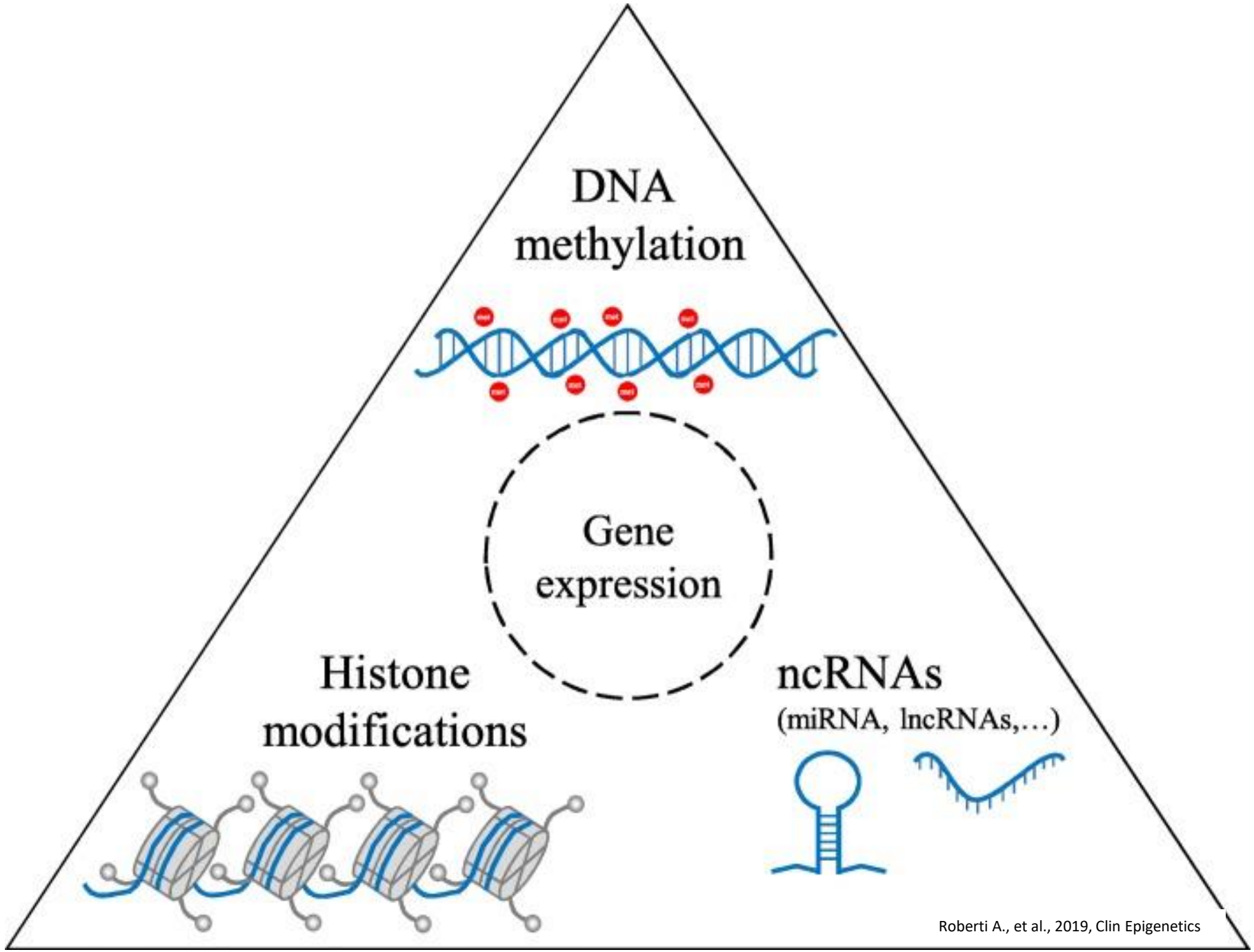


Figure 2. Evidence for epigenetic modulation in pain. Evidence has been obtained for such modulation at four different levels, numbered here in order from peripheral to central. 1, Pain-associated hyperacetylation of *MIP2* and *CXCR5* in the nerve after partial sciatic nerve ligation (PSL) [86] (shown in yellow). 2, Decreased expression of MeCP2 target genes after CFA [91]; miRNA expression changes [104,106]; intrathecal HDAC inhibitor treatment reduces acute pain after CFA [83] (shown in green). 3, *GAD2* hypoacetylation after CFA leads to loss of descending inhibition [84] (shown in pink). 4, Carrageenan-associated miRNA dysregulation in the prefrontal cortex [105] (shown in purple).



Roberti A., et al., 2019, Clin Epigenetics