NIH Public Access
Author Manuscript
Pain Med. Author manuscript; available in PMC 2013 November 01.

Published in final edited form as:
Pain Med. 2012 November ; 13(11): 1474–1490. doi:10.1111/j.1526-4637.2012.01488.x.

Epigenetics and the Transition from Acute to Chronic Pain

Thomas Buchheit, MD,
Duke University Medical Center, Department of Anesthesiology, Durham VA Medical Center, Durham, NC 27710

Thomas Van de Ven, MD, PhD, and
Duke University Medical Center, Department of Anesthesiology, Durham VA Medical Center, Durham, NC 27710

Andrew Shaw, MB, FRCA, FCCM
Duke University Medical Center, Department of Anesthesiology, Durham VA Medical Center, Durham, NC 27710

Abstract

Objective—To review the epigenetic modifications involved in the transition from acute to chronic pain and to identify potential targets for the development of novel, individualized pain therapeutics.

Background—Epigenetics is the study of heritable modifications in gene expression and phenotype that do not require a change in genetic sequence to manifest their effects. Environmental toxins, medications, diet, and psychological stresses can alter epigenetic processes such as DNA methylation, histone acetylation, and RNA interference. Since epigenetic modifications potentially play an important role in inflammatory cytokine metabolism, steroid responsiveness, and opioid sensitivity, they are likely key factors in the development of chronic pain. Although our knowledge of the human genetic code and disease-associated polymorphisms has grown significantly in the past decade, we have not yet been able to elucidate the mechanisms that lead to the development of persistent pain after nerve injury or surgery.

Design—Focused literature review

Results—Significant laboratory and clinical data support the notion that epigenetic modifications are affected by the environment and lead to differential gene expression. Similar to mechanisms involved in the development of cancer, neurodegenerative disease, and inflammatory disorders, the literature endorses an important potential role for epigenetics in chronic pain.

Conclusions—Epigenetic analysis may identify mechanisms critical to the development of chronic pain after injury, and may provide new pathways and target mechanisms for future drug development and individualized medicine.

Keywords

Epigenetics; Pain; DNA Methylation; Histone Deacetylase Inhibitors; RNA interference

Corresponding author: Thomas Buchheit, MD, Duke University Medical Center, Department of Anesthesiology, Durham VA Medical Center, Durham, NC 27710, Office: (919) 286-6938, Fax: (919) 286-6853, Thomas.Buchheit@duke.edu.

Conflict of interest/disclosure:
The authors report no conflicts of interest.

Authors' Contribution
TB, TV, and AS conceived of, wrote, and performed final editing of this manuscript. Medical illustrations were created in collaboration with Stan Coffman from Medmedia Solutions, Durham, NC. We also wish to thank Kathy Gage BS, Duke University Department of Anesthesiology, for her editorial assistance in the preparation of this work.

$watermark-text
$watermark-text
$watermark-text

$watermark-text

$watermark-text

$watermark-text

Introduction

In recent years, we have developed a better understanding of the cellular mechanisms that link inflammation, peripheral sensitization, and pain(1). In addition, we have learned more about the human genetic code(2) and mutations (particularly single nucleotide polymorphisms (SNPs) and copy number variations (CNVs)) that are associated with specific chronic pain syndromes(3, 4). These physiologic and genetic advances, however, do not fully explain why one patient develops chronic pain following an injury, and another patient does not. Despite recent improvements in techniques for acute pain management, 30%–50% of patients still develop chronic pain following surgeries such as amputation, thoracotomy, hernia repair, and mastectomy(5).

It is also notable that monozygotic twins may exhibit significantly different inflammatory and chronic pain phenotypes (6–8), indicating that the etiological basis of these disorders is not due simply to differences in genetic sequence. We now appreciate that response to injury is determined by complex interactions between the genome and the environment. These alterations might well be epigenetic in nature, ie, heritable modifications that are not intrinsic to the genetic code, but that affect gene expression in a tissue-specific manner, resulting in an observable phenotype (Figure 3)(9).

Epigenetic processes are responsible for cellular differentiation during embryogenesis and are critical for normal development(10). These processes also play an important role in memory formation, as correlations between hippocampal activity, DNA methylation, and histone phosphorylation in the brain have been found(11, 12). The spinal cord sensitization seen in painful conditions shares common mechanisms with the neural plasticity of memory formation(13), and it is likely that similar epigenetic mechanisms regulate both of these neural processes.

Multiple examples of the importance of epigenetic influences in development are found throughout nature. One of the best-described cases of environmental influence on gene expression involves the control of bee development by ingesting Royal Jelly. This nutritive substance induces changes in juvenile bee DNA methylation patterns and leads to development of the bee's phenotype to become a queen rather than a worker(14). The concepts of epigenetic heritability and stability have also been described in plants(15) and mammals(16). For instance, high-fat diets fed to paternal rats induce functional changes in β-islet cells of female offspring(16). Similar modifications in DNA methylation were noted in the fathers and offspring, suggesting the non-genetic heritability of this metabolic disorder.

Non-developmental epigenetic modifications are also triggered by environment, nutrition, and stress(17–19), and may play a role in the onset of chronic pain following nerve injury(20, 21). We have long appreciated the importance of the psychosocial environment to the incidence and severity of chronic pain(22–27), and mounting evidence suggests that epigenetic mechanisms supply the link between disease expression and environment(18, 28). Non-genetic factors are important in the development of cancer(29, 30), neurologic disorders(31), and painful disorders such as bladder pain syndromes(7), myofascial pain(32), and temporomandibular joint pain(8). Twin-disease models of neurodegenerative conditions(33), inflammatory periodontal disease(34), and autoimmune disease(35) demonstrate variable disease expression depending on the DNA methylation pattern(6).

Environmental factors alter gene expression and phenotype for painful disorders by inducing epigenetic modifications such as histone acetylation, DNA methylation, and RNA interference(36–38). Following injury, expression of transcription factors such as nuclear

factor-κB (NF-κB) is increased(39), sodium channels in the injured axon are upregulated(40), μ-opioid receptors in the dorsal root ganglion are downregulated(41, 42), substance P expression is altered(43), and the dorsal horn of the spinal cord is structurally reorganized through axonal sprouting(44). As with DNA variation, epigenetic modifications may be inherited and may be propagated over multiple cell divisions; however, they are flexible enough to respond to modifying influences. This concept may in part explain how we interact with our environment at the (epi)genomic level, and is potentially of great importance in understanding the relationship between gene expression and complex diseases such as chronic pain.

Genetics, Epigenetics, and Pain

Over the past several decades, much has been written about the association of genetic polymorphisms and the development of chronic pain(45, 46). It was believed that, through knowledge of genetic variation, we could develop the foundation for individualized medicine that optimizes therapy for each patient based on his/her specific genetic sequence (47). Expectations for personalized medicine were high after completion of the human genome project(2), but thus far, our ability to use the genetic code to prevent or improve chronic pain has been somewhat limited(48). It is the heretofore unquantifiable environmental effect that has been one of the limitations of genetic studies(45).

Multiple candidate gene association studies (CGAS) have been used for the investigation of pain, but have been limited by their focus on genomic regions where the pathophysiology is thought to be reasonably well understood. They are not designed to analyze painful conditions that result from interactions of multiple genes(49). A few candidate gene polymorphisms have been linked to pain susceptibility, including Catechol-O-methyltranferase(COMT). This gene modulates nociceptive and inflammatory pain and has been linked to temporomandibular joint pain syndromes(50). Even studies of COMT, however, have demonstrated inconsistencies. Some investigators have found an association between a COMT single nucleotide polymorphism (COMT SNP val158met)(4, 50) with increasing pain responses, while others failed to replicate these findings(51, 52).

The SCN9A gene has also been studied as a marker for pain sensitivity. Mutations in this gene, which codes for the alpha-subunit of a voltage-gated sodium channel ($Na_v1.7$), are known to result in alterations of pain perception(53), and have been noted in rare pain disorders such as erythromelalgia and paroxysmal extreme pain disorder(54, 55). SCN9A polymorphisms have also been described in individuals who are insensitive to pain(3, 56). Although the implications of the SCN9A gene polymorphism are clear, clinical applications of this knowledge remain limited(47).

Genome-wide association studies (GWAS) have been used in an attempt to overcome some of the limitations of candidate gene analysis. These studies tell us where the genetic variation exists, but do not always fully explain the underlying biology. Furthermore, although GWAS have identified thousands of genetic variations in complex diseases, most of the variants confer only a modest risk with an odds ratio for disease of < 1.5. These genetic variants, therefore, account for only a small fraction of the population attributable risk for heritable complex traits(57, 58), implying a strong non-genetic predisposition to disease. GWAS directed toward painful conditions remain limited in number(45).

$watermark-text $watermark-text $watermark-text

$watermark-text

$watermark-text

$watermark-text

Specific Epigenetic Modifications

Histone modifications

Histones octamers and their surrounding DNA form a nucleosome, the fundamental building block of chromatin (Figure 1A). The N-terminal histone tails may be modified by more than 100 different post-translational processes including acetylation, phosphorylation, and methylation (Figure 1B). Most of the histone complex is inaccessible, but the N-terminal tail protrudes from the nucleosome and is therefore subject to additions that change the three-dimensional chromatin structure and subsequent gene expression(59, 60). One of the more common modifications involves acetylation. Histone acetyl transferases (HAT) add acetyl groups, altering the histone protein structure. This change prevents the chromatin from becoming more compact, allowing transcription factors to bind more easily. This state of increased acetylation and “permissive chromatin” generally increases transcription activity and RNA production from that genetic sequence, especially when located in gene promoter regions(61, 62). Conversely, histone deacetylases (HDACs) remove acetyl groups from histones, generally suppressing gene expression. In concert, these activities serve important regulatory functions.

DNA methylation

Another ubiquitous epigenetic modification involves methylation of DNA cytosine nucleotides. In this process, DNA methyltransferase enzymes (DNMT1, DNMT3A, and DNMT3B) add a methyl group to the 5′carbon of the cytosine pyrimidine ring, converting it to 5-methylcytosine. This methylation generally silences gene expression either by preventing the binding of transcription factors(63, 64), or by attracting methylated DNA-binding proteins such as MeCP2 that themselves repress transcription(Figure 1C)(65, 66). The methylation process is vital for normal embryonic development and growth(67), and these methylation patterns are propagated during cell division.

The degree of cytosine methylation tends to mirror the degree of tissue specialization. For instance, DNA in neurologic tissue is highly methylated, while sperm DNA is relatively unmethylated(68). More recent research has focused on the regulatory importance of cytosine methylation in promoter regions where methylation may silence a previously active gene sequence in the process of tissue specialization(69). In addition to the cytosine nucleotides dispersed throughout the genome, there are “CpG islands” that contain regions rich in cytosine-phosphate-guanine linear sequences(70). These “CpG islands” are found in promoter regions or first exons of approximately 60% of human genes, and are often unmethylated during development, allowing a transcriptionally active state(71). Although promoter site methylation may silence gene expression during development, genes may still be re-activated even in specialized neurologic tissues(72, 73). This potentially modifiable plasticity of neural tissue methylation may hold promise for reversing the neurologic molecular remodeling that occurs during the transition from acute to chronic pain.

Several disease states, including cancer, schizophrenia, and opioid addiction, are associated with DNA methylation abnormalities(30, 74–76). In cancer, these altered methylation patterns may lead to tumor growth by downregulating tumor suppressor genes(30). Methylated gene domains demonstrate not only stability, but also heritability(70). The epigenetic influence across generations is demonstrated in rodent studies in which spermatogenesis is suppressed, and methylation patterns are altered for several generations after using the anti-androgenic compound vinclozolin during embryonic development(77).

$watermark-text

$watermark-text

$watermark-text

Non-coding RNA

Gene expression can also be controlled by RNA interference, which involves endogenous molecules such as small interfering RNA (siRNA), microRNA (miRNA), and short hairpin RNA (shRNA). These small non-coding RNA molecules can silence gene expression by binding to mRNA and inducing subsequent degradation of the direct gene product (Figure 1D)(78). These molecules can self-propagate through cell division and epigenetically transmit regulatory information across generations(79). Interfering RNAs carry great therapeutic promise and have been used in animal trials for chronic neuropathic pain(80) and neurodegenerative disease(81), as well as in human clinical trials for cancer(82).

Our understanding of epigenetic processes has increased dramatically over the past decade. Efforts are currently underway, through such groups as the International Human Epigenome Consortium, to sequence and create maps of cell-specific DNA methylation and histone modifications(83).

Techniques of Epigenetic Analysis

There are many challenges in defining the specific epigenetic changes that lead to a particular disease state. Many earlier epigenomic studies have been limited by either inadequate genome survey or small sample size, and the relationship in many diseases between phenotypic expression and epigenomic variation remains unclear(84). It is unlikely that single gene epigenetic modification will explain the complex pain phenotypes seen after injury or surgery. Epigenome-wide association studies have been proposed as a possible solution to improve our understanding of the links between disease state and epigenetic modifications. Comprehensive epigenomic maps are currently being developed with promising future applications(84).

Another challenge with epigenetic studies and disease variation is need for enhanced comprehension of the distinction between cause and consequence(84). To fully understand if a particular biomarker represents the cause OF a disease or the effect FROM a disease, we will need to perform analyses at multiple time points before and after the development of a disease. This initiative has already begun with the establishment of the US National Institutes of Health Roadmap Epigenomics Mapping Consortium(85).

Regardless of the relationship between biomarkers and causation, however, epigenetic modifications throughout the course of a chronic disease can be used as biomarkers. In particular, DNA methylation is well suited as a potential predictive biomarker secondary to its relative chemical stability. Reliable biomarkers are critical if we are to develop personalized epigenetic interventions. Candidate markers would need to be found in an accessible space (blood), but still reflect the neurobiological process occurring at the proximal tissue (spinal cord/brain). Whether the circulating leukocyte epigenome can report on more inaccessible tissues (such as CNS) is uncertain, but there is growing evidence that methylation patterns tend to be similar between proximal tissue and more easily accessible circulating blood cells. For example, it was recently shown that the pattern of CpG island methylation in the promoter region of the prodynorphin gene in both human brain tissue collected post-mortem and matched peripheral blood mononuclear cells is virtually identical (86).

The burgeoning field of epigenetics is using novel technologies to measure these heritable, yet modifiable, patterns of transcriptional regulation. DNA methylation is analyzed through bisulfite sequencing which allows the epigenetic information present in the form of cytosine methylation to be retained during amplification (Figure 2B). Traditional molecular analysis of specific gene loci relies on the ability to amplify the DNA of interest using cloning and

$watermark-text

$watermark-text

$watermark-text

polymerase chain reaction (PCR) techniques. If this amplification is done, however, without somehow immortalizing the methylation status of a particular cytosine, that information will be lost after the first PCR cycle. To solve this problem, unmethylated cytosines can be modified through the bisulfite reaction, deaminating them to uracil. Methylated cytosines, however, are not deaminated by bisulfite, remaining unchanged during subsequent amplification. Probes can then be designed to determine whether a specific promoter region has retained a particular cytosine (previously methylated) or whether this cytosine has been converted to uracil (previously unmethylated). The methylation status of the promoter can then be determined using the cytosine/uracil ratio.

Histone protein modifications have also been studied since 1988 through a process of chromatin immunoprecipitation (ChIP) (Figure 2A)(87). This process involves fragmentation of the chromatin and immunoprecipitation using an antibody to the protein or modification of interest. For example, an antibody to a specific acetylation site on histone H3 is used to precipitate all DNA associated with that particular acetylated histone. Following immunoprecipitation, the DNA fragments are then typically identified through microarray hybridization. More recently, “next generation sequencing” (NGS) technologies have been combined with ChIP (ChIP-seq), providing a high resolution, genome wide analysis of histone modification. Whereas microarray techniques analyze regions of the genome previously identified, NGS carries the possibility of capturing all the DNA fragments isolated by immunoprecipitation(71). These NGS technologies will continue to expand our understanding of epigenetic changes and the chromatin regulatory state throughout the genome.

The Role of Epigenetic Modification in the Transition from Acute to Chronic Pain

Prevention of chronic pain after injury has been the focus of numerous previous trials involving interventions such as multimodal analgesics and catheter-based local anesthetic infusions(88–90). Although these techniques are successful in reducing the burden of acute pain(91), they have not succeeded in dramatically reducing the incidence of chronic post-injury or post-surgical pain(92–94). The shortcomings of our preventive strategies are most pronounced following surgeries that have a higher risk for developing chronic pain such as amputation, thoracotomy, hernia repair, coronary artery bypass, and mastectomy(5, 95, 96).

Our therapeutic limitations may be partially due to our inability to prevent the epigenetic changes that occur following injury and surgery. A patient’s gene expression profile changes rapidly in the post-injury period(97), with over 1,000 genes activated in the dorsal root ganglion alone after nerve injury(98). There is significant evidence for epigenetic control of this gene activation in the transition from acute to chronic pain. First, immunologic response and inflammatory cytokine expression are under epigenetic control(99, 100). Secondly, glucocorticoid receptor (GR) function, which affects pain sensitivity, inflammation, and the development of autoimmune disease, is modulated both through post-translational mechanisms and DNA methylation(101–103). Thirdly, genes such as glutamic acid decarboxylase 65 (GAD65) that code for pain regulatory enzymes in the central nervous system are known to be hypoacetylated and downregulated in inflammatory and nerve injury pain states(104). Finally, epigenetic modifications are involved in opioid receptor regulation and function, with implications for endogenous pain modulation systems and pain severity(63, 76).

The important link between epigenetic regulation and pain is also supported by studies involving intervertebral disc degeneration and chronic low back pain. Tajerian et al found that DNA methylation of an extracellular matrix protein SPARC (Secreted Protein, Acidic,

$watermark-text

$watermark-text

$watermark-text

Rich in Cysteine) is linked to accelerated disc degeneration both in humans and in animal models of this disease(38). The correlation between pain and epigenetics is additionally observed in a study of DNA methylation in human cancer where EDNRB (the gene that codes for endothelin receptor type B) is heavily methylated and downregulated in painful squamous cell carcinoma (SCC) lesions(105). The investigators noted similar findings in their mouse model of SCC, and were able to improve mechanical allodynia when EDNRB transcription was virally augmented(105). These human and animal studies strongly support a role for gene methylation in regulating the pain experience.

Cytokines

Injury and autoimmune disease are characterized by excessive cytokine production, and anti-cytokine therapies have been successfully used to treat painful conditions such as ankylosing spondylitis(106, 107) and neuropathy(108, 109). The link between cytokine expression and pain is supported by the demonstration of T-cell infiltration and inflammatory interleukin (IL) release in animal models of neuropathic pain(110). Furthermore, interventions that modify the immune response to injury also reduce pain. Such modifications include depletion of mast cells(111), reduction of peripheral macrophages using clodronate(112), and impairment of complement activation and neutrophil chemotaxis(113).

One of the inflammatory master switches, nuclear factor-κB (NF-κB), induces multiple cytokines(114) and cyclo-oxygenase(115). NF-κB is epigenetically regulated by acetylation and remodeling of chromatin(114, 116, 117). When activated, this transcription factor demethylates and induces cytokines such as TNF-α, IL-1, IL-2, and IL-6(118, 119). Activation of NF-κB is associated with autoimmune and neurodegenerative disease(120). Conversely, inhibition of NF-κB reduces pain behavior after peripheral nerve injury(121).

The link between epigenetically-induced cytokine production and pain intensity has been noted in multiple disease models such as migraine headache(122), diabetes(114), and osteoarthritis(99). In osteoarthritis, DNA demethylation at specific CpG sites in human chrondrocytes produces aberrant expression of inflammatory cytokines (IL-1β) and metalloproteinases(99). Thus, cytokine-induced painful joint damage appears to be epigenetically modulated.

Glucocorticoid Receptors

Glucocorticoids are important endogenous regulators that appear to protect against excessive inflammatory response following injury. Stress-induced glucocorticoid production suppresses immune cell release of IL-6, TNF-α, and other inflammatory cytokines(123). Exogenous glucocorticoids also have potent anti-inflammatory actions and are used extensively in the treatment of autoimmune disease and painful conditions. However, not all patients respond equally to their clinical effects, and it is believed that glucocorticoid resistance is a likely mechanism in the development of autoimmune disease and chronic pain(124).

The glucocorticoid receptor (GR) is controlled by a system of complex regulatory mechanisms, and clinical response to glucocorticoids correlates with the number of intracellular GRs(125). Normally, individuals demonstrate variable GR promoter methylation(103) and variable response to glucocorticoid therapy(126). Diverse methylation patterns are believed to lead to the use of alternative promoter sites and subsequent alteration in GR sensitivity(103).

GR expression is also modified by maternal care, grooming, diet(127, 128), and early-life stresses(129, 130). Human studies have demonstrated epigenetic alterations in

glucocorticoid receptors of patients who previously suffered abuse(131). The style of maternal care appears to specifically affect methylation patterns of exon 17 of the GR promoter, epigenetically linking receptor function and early-life experience(132). Abnormalities in GR-mediated immune cell function may lead to the development of inflammatory adult phenotypes(133) and autoimmune disorders such as rheumatoid arthritis(101, 134). GR dysfunction may also play a role in fatigue, chronic pain states, and fibromyalgia(102, 135). These maternally influenced expression patterns, however, are not necessarily permanent and have been reversed in cross-fostering parent studies(136). The GR appears to provide a potential link between injury, environmental stresses, and the severity of chronic pain.

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.

“Epigenetic Intervention” to Prevent Chronic Pain

Genetic studies have taught us that variability in pain sensitivity results from multiple genetic and environmental factors. Environmental influences upon pain severity have been previously described and linked to early-life stress(47, 140–143). Although precise mechanisms have yet to be elucidated, epigenetic modifications are increasingly appreciated as a likely factor in this linkage(36, 104, 122).

Our need for targeted therapies has never been greater. Multiple analgesic drugs are now in use; however, most of these share a common function with opioids or anti-inflammatory medications. These medications have improved symptoms in some patients, but have created the additional morbidities of systemic toxicity, opioid tolerance, and addiction. Our options for safe and effective treatments for chronic pain remain limited with few recent “breakthroughs.”

Since the sequencing of the human genome, there have been increasing calls for “personalized medicine” that tailors drug therapy to a patient’s pain phenotype(47, 144). Although such therapies have demonstrated some efficacy as cancer treatments(145–147), we have not yet had great success with targeted pain therapies. We will now review some of the potential targets for “personalized epigenetic intervention.”

Intervention: HDAC Inhibition

Given the association between histone deacetylation and cancer, neurodegenerative disease, and pain, histone deacetylase inhibitors (HDACis) have been evaluated as therapeutic agents for these diseases(30, 36, 148). Thus far, HDACis are primarily used in cancer therapy. In these patients, HDACis alter the balance of acetylation/deacetylation and activate genes that

$watermark-text $watermark-text $watermark-text

$watermark-text

$watermark-text

$watermark-text

suppress tumor growth and invasion(30, 149–152). In neurodegenerative disease, HDACis have been evaluated secondary to their ability to induce neural growth and to improve memory(153). HDACis have also demonstrated evidence for analgesia in both inflammatory and neuropathic pain(151, 154, 155). The clinical effect of many of these drugs is thought to be partially attributed to reduced production of inflammatory cytokines such as TNF-α and IL-1β(156).

HDACis are organized into several different structural groups. Trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA) are hydroxamate-based HDACis. TSA inhibits both class 1 (ubiquitously expressed) and class 2 (selectively expressed) HDACs, whereas SAHA exhibits greater selectivity for class 1 HDAC. TSA produces analgesia in animal models with an associated decrease in expression of transient receptor potential type-1 cation channel (Trpv1) and protein kinase Cε (PKCε)(157). SAHA reduces the nociceptive response of animals during the second phase of the formalin test(154). These drugs increase acetylation of the transcription factor p65/Re1A, which enhances gene expression of the metabotrobic glutamate receptors (mGlu2) in dorsal root ganglia neurons. Activation of these mGlu2 receptors inhibits primary afferent neurotransmitter release in the dorsal horn of the spinal cord and provides analgesia in animal models of neuropathic pain(158). TSA also enhances μ-opioid receptor transcription(159), indicating partial HDAC modulation of the endogenous opioid system.

Another HDACi, Givinostat, has not only demonstrated evidence of analgesia in animal models, but also efficacy in a human trial for juvenile idiopathic arthritis. Although randomized studies have not yet been performed, its use for this autoimmune inflammatory disease is especially encouraging given its relative lack of systemic toxicity(160).

The most commonly used HDACi, Valproic acid (VPA), is part of the aliphatic-based drug class that inhibits class I and II HDACs(151, 161), and is effective following systemic or intrathecal administration(162, 163). VPA is of particular interest because it has been successful with long-term clinical use(164). Although it is now used predominantly to treat chronic painful conditions(163–165), its inhibition of HDAC and potential to prevent specific epigenetic alterations may lead to preemptive use in the acute setting. It is not yet clear whether VPA-induced analgesia results from HDAC inhibition or its ability to potentiate gamma amino butyric acid (GABA) in the central nervous system.

Although therapies based on HDAC inhibition have been effective in treating pain and oncologic disease, non-specific HDACis such as TSA affect the regulation of multiple genes, which increases the possibility of side effects with this therapy(166, 167). The success of future drug development will likely depend upon our ability to target specific subclasses of HDACs that selectively alter pain processing without the toxicities of non-selective agents. The importance of this selectivity concept has been demonstrated in a mouse model in which a full knockout of the HDAC4 gene (a Class IIa HDAC) is lethal, whereas a conditional knockout of this gene provides analgesia(168). Further investigations of HDAC subclass function are needed in order to identify novel drug targets.

Intervention: DNA Methylation

DNA methylation is another key epigenetic mechanism. Methylation patterns, although generally stable throughout the genome, are responsive to pharmacologic intervention. One common medication that appears to act through epigenetic mechanisms is glucosamine(169). In arthritis models, it has been demonstrated that glucosamine prevents demethylation of the IL-1β gene promoter, thereby decreasing expression of this cytokine. Decreased IL-1β subsequently reduces NF-κB expression and downstream inflammatory cytokine production(119, 170).

$watermark-text

$watermark-text

$watermark-text

In addition to its function as an HDAC inhibitor, VPA induces demethylation of multiple genes(171). One of these important genes encodes for Reelin, a glycoprotein synthesized by GABAergic neurons of the central nervous system(172, 173). Reelin modulates N-methyl-D-aspartate (NMDA) receptor function(174), and is important for sensory processing(175). Mutations of this gene cause alterations in mechanical and thermal hypersensitivity(173), which indicates the potential significance of VPA regulation of Reelin in the development of chronic pain.

L-methionine administration has also been tested as a potential drug for epigenetic intervention. This amino acid appears to increase methylation patterns of the glucocorticoid receptor gene, thereby altering the hypothalamic-pituitary-adrenal (HPA) response to stress(176). In addition, dietary methyl supplementation in an animal model improves the health and longevity of offspring(177). Both of these findings suggest that nutritional status partially controls the activity of the glucocorticoid receptor and its role in inflammatory disease.

The combined action of pharmacologic DNA demethylation and HDAC inhibition increases activity at the proximal promoter site of the μ-opioid receptor gene, increasing μ-opioid receptor expression(137). Carried out in concert, these processes may represent an important balance that allows less stable histone modifications to lead to more stable changes in DNA methylation, thus facilitating longer-term modifications in the endogenous opioid receptor system.

Intervention: RNA Interference

Epigenetic therapies based on RNA interference (RNAi) also hold promise for preventing and treating chronic pain. These methods target specific disease pathways.

RNAi is an endogenous mechanism for gene silencing in plants(178) and mammals(179), and involves subgroups such as small interfering RNA (siRNA), microRNA (miRNA), and short hairpin RNA (shRNA). Given their ability to silence undesirable gene products in malignancy, these small RNA molecules have been used for cancer therapy(82). They have also been shown to improve chronic neuropathic pain(80).

SiRNA targeted for the NR2 subunit of NMDA receptors abolishes formalin-induced pain behavior in rats(180). Likewise, injection of siRNA aimed at the NR1 subunit of the NMDA receptor alleviates experimentally induced allodynia in mice(181). Successful RNA interference studies have targeted TRPV1 channels(182), brain-derived neurotrophic factor(183), cytokines such as TNF-α(184), and pain-related cation channels ($P2X_3$)(80). Importantly, direct intrathecal administration of siRNA targeting $P2X_3$ in animals has not demonstrated significant toxicity(80), indicating that this intervention may be applicable to humans in coming years.

Conclusions

The transition from acute to chronic pain is a complex process involving local inflammation and nociceptor activation that may resolve in some patients and may lead to the development of chronic pain in others. As we learn more about the various ways that injury and environment change gene expression, we can begin to elucidate disease mechanisms and gain insight into potential therapies. Epigenetic alterations such as DNA methylation, histone acetylation, and RNA interference are necessary for normal tissue specialization and neurologic development. However, these same modifications play a significant role in the induction of the chronic pain phenotype following neurologic injury.

In contrast to the genetic determinism inherent in genomic studies, the field of epigenetics strives to understand the environmental control over gene expression. Such knowledge will open up opportunities for developing novel analgesics. Future personalized therapies will likely be based on epigenetic interventions that alter the transcriptional expression that occurs in chronic pain states. Given the strong mechanistic implications of epigenetic modifications in the development of chronic pain, and our current treatment limitations, we possess both the promise of epigenetic tools and the imperative to prevent the transition from acute to chronic pain.

Acknowledgments

Financial Support:

Dr. Shaw and Dr. Buchheit are supported by the Congressionally Directed Medical Research Programs and the Department of Defense(DM102142). Dr. Van de Ven is supported by T32 NIH grant# 2T32GM008600.

References

1. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009 Oct 16; 139(2):267–84. [PubMed: 19837031]
2. Schuler GD, Boguski MS, Stewart EA, Stein LD, Gyapay G, Rice K, et al. A gene map of the human genome. Science. 1996 Oct 25; 274(5287):540–6. [PubMed: 8849440]
3. Yuan R, Zhang X, Deng Q, Si D, Wu Y, Gao F, et al. Two Novel SCN9A Gene Heterozygous Mutations May Cause Partial Deletion of Pain Perception. Pain medicine. 2011 Oct; 12(10):1510–4. [PubMed: 21939494]
4. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science. 2003 Feb 21; 299(5610): 1240–3. [PubMed: 12595695]
5. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006 May 13; 367(9522):1618–25. [PubMed: 16698416]
6. Javierre BM, Fernandez AF, Richter J, Al-Shahrour F, Martin-Subero JI, Rodriguez-Ubreva J, et al. Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. Genome Res. 2010 Feb; 20(2):170–9. [PubMed: 20028698]
7. Altman D, Lundholm C, Milsom I, Peeker R, Fall M, Iliadou AN, et al. The genetic and environmental contribution to the occurrence of bladder pain syndrome: an empirical approach in a nationwide population sample. Eur Urol. 2011 Feb; 59(2):280–5. [PubMed: 21056533]
8. Michalowicz BS, Pihlstrom BL, Hodges JS, Bouchard TJ Jr. No heritability of temporomandibular joint signs and symptoms. J Dent Res. 2000 Aug; 79(8):1573–8. [PubMed: 11023277]
9. Villeneuve LM, Natarajan R. Epigenetic mechanisms. Contrib Nephrol. 2011; 170:57–65. [PubMed: 21659758]
10. Sassone-Corsi P. Unique chromatin remodeling and transcriptional regulation in spermatogenesis. Science. 2002 Jun 21; 296(5576):2176–8. [Review]. [PubMed: 12077401]
11. Guo JU, Ma DK, Mo H, Ball MP, Jang MH, Bonaguidi MA, et al. Neuronal activity modifies the DNA methylation landscape in the adult brain. Nat Neurosci. 2011 Oct; 14(10):1345–51. [PubMed: 21874013]
12. Chwang WB, Arthur JS, Schumacher A, Sweatt JD. The nuclear kinase mitogen- and stress-activated protein kinase 1 regulates hippocampal chromatin remodeling in memory formation. J Neurosci. 2007 Nov 14; 27(46):12732–42. [PubMed: 18003853]
13. Ji RR, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003 Dec; 26(12):696–705. [PubMed: 14624855]
14. Kucharski R, Maleszka J, Foret S, Maleszka R. Nutritional control of reproductive status in honeybees via DNA methylation. Science. 2008 Mar 28; 319(5871):1827–30. [PubMed: 18339900]

$watermark-text
$watermark-text
$watermark-text

$watermark-text

$watermark-text

$watermark-text

15. Cubas P, Vincent C, Coen E. An epigenetic mutation responsible for natural variation in floral symmetry. Nature. 1999 Sep 9; 401(6749):157–61. [PubMed: 10490023]
16. Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. Nature. 2010 Oct 21; 467(7318):963–6. [PubMed: 20962845]
17. Coppede F. The complex relationship between folate/homocysteine metabolism and risk of Down syndrome. Mutat Res. 2009 Jul-Aug;682(1):54–70. [PubMed: 19524060]
18. Bell CG, Beck S. The epigenomic interface between genome and environment in common complex diseases. Brief Funct Genomics. 2010 Dec; 9(5–6):477–85. [PubMed: 21062751]
19. McEwen BS, Eiland L, Hunter RG, Miller MM. Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology. 2012 Jan; 62(1):3–12. [PubMed: 21807003]
20. Kiguchi N, Kobayashi Y, Maeda T, Fukazawa Y, Tohya K, Kimura M, et al. Epigenetic augmentation of the MIP-2/CXCR2 axis through histone H3 acetylation in injured peripheral nerves elicits neuropathic pain. J Pharmacol Exp Ther. 2011 Dec 1.
21. Uchida H, Sasaki K, Ma L, Ueda H. Neuron-restrictive silencer factor causes epigenetic silencing of Kv4.3 gene after peripheral nerve injury. Neuroscience. 2010 Mar 10; 166(1):1–4. [PubMed: 20006971]
22. Katz J, Poleshuck EL, Andrus CH, Hogan LA, Jung BF, Kulick DI, et al. Risk factors for acute pain and its persistence following breast cancer surgery. Pain. 2005 Dec 15; 119(1–3):16–25. [PubMed: 16298063]
23. Caumo W, Schmidt AP, Schneider CN, Bergmann J, Iwamoto CW, Adamatti LC, et al. Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. Acta anaesthesiologica Scandinavica. 2002 Nov; 46(10):1265–71. [PubMed: 12421200]
24. Bosmans JC, Geertzen JH, Post WJ, van der Schans CP, Dijkstra PU. Factors associated with phantom limb pain: a 31/2-year prospective study. Clin Rehabil. 2010 May; 24(5):444–53. [PubMed: 20442256]
25. Dijkstra PU, Geertzen JH, Stewart R, van der Schans CP. Phantom pain and risk factors: a multivariate analysis. J Pain Symptom Manage. 2002 Dec; 24(6):578–85. [PubMed: 12551807]
26. Ephraim PL, Wegener ST, MacKenzie EJ, Dillingham TR, Pezzin LE. Phantom pain, residual limb pain, and back pain in amputees: results of a national survey. Arch Phys Med Rehabil. 2005 Oct; 86(10):1910–9. [PubMed: 16213230]
27. Nikolajsen L, Ilkjaer S, Kroner K, Christensen JH, Jensen TS. The influence of preamputation pain on postamputation stump and phantom pain. Pain. 1997 Sep; 72(3):393–405. [PubMed: 9313280]
28. Petronis A. Epigenetics as a unifying principle in the aetiology of complex traits and diseases. Nature. 2010 Jun 10; 465(7299):721–7. [PubMed: 20535201]
29. Bollati V, Baccarelli A, Hou L, Bonzini M, Fustinoni S, Cavallo D, et al. Changes in DNA methylation patterns in subjects exposed to low-dose benzene. Cancer Res. 2007 Feb 1; 67(3): 876–80. [PubMed: 17283117]
30. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010 Jan; 31(1):27–36. [Review]. [PubMed: 19752007]
31. Sananbenesi F, Fischer A. The epigenetic bottleneck of neurodegenerative and psychiatric diseases. Biol Chem. 2009 Nov; 390(11):1145–53. [PubMed: 19747081]
32. Schmitter M, Keller L, Giannakopoulos N, Rammelsberg P. Chronic stress in myofascial pain patients. Clin Oral Investig. 2010 Oct; 14(5):593–7.
33. Rieley MB, Stevenson DA, Viskochil DH, Tinkle BT, Martin LJ, Schorry EK. Variable expression of neurofibromatosis 1 in monozygotic twins. Am J Med Genet A. 2011 Mar; 155A(3):478–85. [PubMed: 21337692]
34. Torres de Heens GL, Loos BG, van der Velden U. Monozygotic twins are discordant for chronic periodontitis: clinical and bacteriological findings. J Clin Periodontol. 2010 Feb; 37(2):120–8. [PubMed: 20653816]
35. Ballestar E. Epigenetics lessons from twins: prospects for autoimmune disease. Clin Rev Allergy Immunol. 2010 Aug; 39(1):30–41. [PubMed: 19653134]

$watermark-text

36. Doehring A, Geisslinger G, Lotsch J. Epigenetics in pain and analgesia: an imminent research field. European journal of pain. 2011 Jan; 15(1):11–6. [PubMed: 20584621]

37. Lacroix-Fralish ML, Tawfik VL, Tanga FY, Spratt KF, DeLeo JA. Differential spinal cord gene expression in rodent models of radicular and neuropathic pain. Anesthesiology. 2006 Jun; 104(6): 1283–92. [PubMed: 16732101]

38. Tajerian M, Alvarado S, Millecamps M, Dashwood T, Anderson KM, Haglund L, et al. DNA methylation of SPARC and chronic low back pain. Mol Pain. 2011; 7:65. [PubMed: 21867537]

39. Ma W, Bisby MA. Increased activation of nuclear factor kappa B in rat lumbar dorsal root ganglion neurons following partial sciatic nerve injuries. Brain research. 1998 Jun 29; 797(2):243–54. [PubMed: 9666140]

40. Jin X, Gereau RWt. Acute p38-mediated modulation of tetrodotoxin-resistant sodium channels in mouse sensory neurons by tumor necrosis factor-alpha. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2006 Jan 4; 26(1):246–55. [PubMed: 16399694]

41. Li Z, Proud D, Zhang C, Wiehler S, McDougall JJ. Chronic arthritis down-regulates peripheral mu-opioid receptor expression with concomitant loss of endomorphin 1 antinociception. Arthritis and rheumatism. 2005 Oct; 52(10):3210–9. [PubMed: 16200625]

42. Porreca F, Tang QB, Bian D, Riedl M, Elde R, Lai J. Spinal opioid mu receptor expression in lumbar spinal cord of rats following nerve injury. Brain Res. 1998 Jun 8; 795(1–2):197–203. [PubMed: 9622629]

43. Ma W, Bisby MA. Partial and complete sciatic nerve injuries induce similar increases of neuropeptide Y and vasoactive intestinal peptide immunoreactivities in primary sensory neurons and their central projections. Neuroscience. 1998 Oct; 86(4):1217–34. [PubMed: 9697128]

44. Okamoto M, Baba H, Goldstein PA, Higashi H, Shimoji K, Yoshimura M. Functional reorganization of sensory pathways in the rat spinal dorsal horn following peripheral nerve injury. J Physiol. 2001 Apr 1; 532(Pt 1):241–50. [PubMed: 11283238]

45. Kim H, Clark D, Dionne RA. Genetic contributions to clinical pain and analgesia: avoiding pitfalls in genetic research. J Pain. 2009 Jul; 10(7):663–93. [PubMed: 19559388]

46. Young EE, Lariviere WR, Belfer I. Genetic basis of pain variability: recent advances. J Med Genet. 2011 Nov 5.

47. Kim H, Dionne RA. Individualized pain medicine. Drug discovery today Therapeutic strategies. 2009; 6(3):83–7. [PubMed: 21399745]

48. Muralidharan A, Smith MT. Pain, analgesia and genetics. J Pharm Pharmacol. 2011 Nov; 63(11): 1387–400. [PubMed: 21988420]

49. Buskila D, Sarzi-Puttini P, Ablin JN. The genetics of fibromyalgia syndrome. Pharmacogenomics. 2007 Jan; 8(1):67–74. [Review]. [PubMed: 17187510]

50. Diatchenko L, Slade GD, Nackley AG, Bhalang K, Sigurdsson A, Belfer I, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet. 2005 Jan 1; 14(1):135–43. [PubMed: 15537663]

51. Armero P, Muriel C, Santos J, Sanchez-Montero FJ, Rodriguez RE, Gonzalez-Sarmiento R. COMT (Val158Met) polymorphism is not associated to neuropathic pain in a Spanish population. European journal of pain. 2005 Jun; 9(3):229–32. [PubMed: 15862471]

52. Kim H, Lee H, Rowan J, Brahim J, Dionne RA. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. Molecular pain. 2006; 2:24. [PubMed: 16848906]

53. Nassar MA, Stirling LC, Forlani G, Baker MD, Matthews EA, Dickenson AH, et al. Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. Proceedings of the National Academy of Sciences of the United States of America. 2004 Aug 24; 101(34):12706–11. [PubMed: 15314237]

54. Reimann F, Cox JJ, Belfer I, Diatchenko L, Zaykin DV, McHale DP, et al. Pain perception is altered by a nucleotide polymorphism in SCN9A. Proc Natl Acad Sci U S A. 2010 Mar 8.

55. Dib-Hajj SD, Yang Y, Waxman SG. Genetics and molecular pathophysiology of Na(v)1.7-related pain syndromes. Adv Genet. 2008; 63:85–110. [PubMed: 19185186]

$watermark-text

$watermark-text

$watermark-text

56. Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature. 2006 Dec 14; 444(7121): 894–8. [PubMed: 17167479]
57. Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH, et al. Missing heritability and strategies for finding the underlying causes of complex disease. Nature reviews Genetics. 2010 Jun; 11(6):446–50.
58. Clarke AJ, Cooper DN. GWAS: heritability missing in action? Eur J Hum Genet. 2010 Aug; 18(8): 859–61. [PubMed: 20234388]
59. Zhou VW, Goren A, Bernstein BE. Charting histone modifications and the functional organization of mammalian genomes. Nat Rev Genet. 2011 Jan; 12(1):7–18. [PubMed: 21116306]
60. Kouzarides T. Chromatin modifications and their function. Cell. 2007 Feb 23; 128(4):693–705. [Review]. [PubMed: 17320507]
61. Struhl K. Histone acetylation and transcriptional regulatory mechanisms. Genes & development. 1998 Mar 1; 12(5):599–606. [Review]. [PubMed: 9499396]
62. Bollati V, Baccarelli A. Environmental epigenetics. Heredity. 2010 Jul; 105(1):105–12. [PubMed: 20179736]
63. Comb M, Goodman HM. CpG methylation inhibits proenkephalin gene expression and binding of the transcription factor AP-2. Nucleic Acids Res. 1990 Jul 11; 18(13):3975–82. [PubMed: 1695733]
64. Watt F, Molloy PL. Cytosine methylation prevents binding to DNA of a HeLa cell transcription factor required for optimal expression of the adenovirus major late promoter. Genes & development. 1988 Sep; 2(9):1136–43. [PubMed: 3192075]
65. Nan X, Campoy FJ, Bird A. MeCP2 is a transcriptional repressor with abundant binding sites in genomic chromatin. Cell. 1997 Feb 21; 88(4):471–81. [PubMed: 9038338]
66. Boyes J, Bird A. DNA methylation inhibits transcription indirectly via a methyl-CpG binding protein. Cell. 1991 Mar 22; 64(6):1123–34. [PubMed: 2004419]
67. Li E, Bestor TH, Jaenisch R. Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. Cell. 1992 Jun 12; 69(6):915–26. [PubMed: 1606615]
68. Ehrlich M, Gama-Sosa MA, Huang LH, Midgett RM, Kuo KC, McCune RA, et al. Amount and distribution of 5-methylcytosine in human DNA from different types of tissues of cells. Nucleic acids research. 1982 Apr 24; 10(8):2709–21. [PubMed: 7079182]
69. Chen ZX, Riggs AD. DNA methylation and demethylation in mammals. J Biol Chem. 2011 May 27; 286(21):18347–53. [PubMed: 21454628]
70. Bird A. Perceptions of epigenetics. Nature. 2007 May 24; 447(7143):396–8. [PubMed: 17522671]
71. Ku CS, Naidoo N, Wu M, Soong R. Studying the epigenome using next generation sequencing. J Med Genet. 2011 Nov; 48(11):721–30. [PubMed: 21825079]
72. Miller CA, Sweatt JD. Covalent modification of DNA regulates memory formation. Neuron. 2007 Mar 15; 53(6):857–69. [PubMed: 17359920]
73. Hsieh CL. Dependence of transcriptional repression on CpG methylation density. Molecular and cellular biology. 1994 Aug; 14(8):5487–94. [PubMed: 7518564]
74. Lubbert M, Oster W, Ludwig WD, Ganser A, Mertelsmann R, Herrmann F. A switch toward demethylation is associated with the expression of myeloperoxidase in acute myeloblastic and promyelocytic leukemias. Blood. 1992 Oct 15; 80(8):2066–73. [PubMed: 1327288]
75. Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A, et al. Reelin promoter hypermethylation in schizophrenia. Proceedings of the National Academy of Sciences of the United States of America. 2005 Jun 28; 102(26):9341–6. [PubMed: 15961543]
76. Nielsen DA, Yuferov V, Hamon S, Jackson C, Ho A, Ott J, et al. Increased OPRM1 DNA methylation in lymphocytes of methadone-maintained former heroin addicts. Neuropsychopharmacology. 2009 Mar; 34(4):867–73. [PubMed: 18650805]
77. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005 Jun 3; 308(5727):1466–9. [PubMed: 15933200]
78. Liang R, Bates DJ, Wang E. Epigenetic Control of MicroRNA Expression and Aging. Curr Genomics. 2009 May; 10(3):184–93. [PubMed: 19881911]

$watermark-text

$watermark-text

$watermark-text

79. Rassoulzadegan M, Grandjean V, Gounon P, Vincent S, Gillot I, Cuzin F. RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. Nature. 2006 May 25; 441(7092): 469–74. [PubMed: 16724059]
80. Dorn G, Patel S, Wotherspoon G, Hemmings-Mieszczak M, Barclay J, Natt FJ, et al. siRNA relieves chronic neuropathic pain. Nucleic Acids Res. 2004; 32(5):e49. [PubMed: 15026538]
81. McBride JL, Pitzer MR, Boudreau RL, Dufour B, Hobbs T, Ojeda SR, et al. Preclinical Safety of RNAi-Mediated HTT Suppression in the Rhesus Macaque as a Potential Therapy for Huntington's Disease. Mol Ther. 2011 Dec; 19(12):2152–62. [PubMed: 22031240]
82. Wang Z, Rao DD, Senzer N, Nemunaitis J. RNA interference and cancer therapy. Pharm Res. 2011 Dec; 28(12):2983–95. [PubMed: 22009588]
83. Time for the epigenome. Nature. 2010 Feb 4.463(7281):587.
84. Rakyan VK, Down TA, Balding DJ, Beck S. Epigenome-wide association studies for common human diseases. Nat Rev Genet. 2011 Aug; 12(8):529–41. [PubMed: 21747404]
85. Bernstein BE, Stamatoyannopoulos JA, Costello JF, Ren B, Milosavljevic A, Meissner A, et al. The NIH Roadmap Epigenomics Mapping Consortium. Nature biotechnology. 2010 Oct; 28(10): 1045–8.
86. Yuferov V, Nielsen DA, Levran O, Randesi M, Hamon S, Ho A, et al. Tissue-specific DNA methylation of the human prodynorphin gene in post-mortem brain tissues and PBMCs. Pharmacogenet Genomics. 2011 Apr; 21(4):185–96. [Research Support, N.I.H., Extramural]. [PubMed: 20808262]
87. Solomon MJ, Larsen PL, Varshavsky A. Mapping protein-DNA interactions in vivo with formaldehyde: evidence that histone H4 is retained on a highly transcribed gene. Cell. 1988 Jun 17; 53(6):937–47. [PubMed: 2454748]
88. Huang YM, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative celecoxib administration for pain management after total knee arthroplasty - a randomized, controlled study. BMC Musculoskelet Disord. 2008; 9:77. [PubMed: 18519002]
89. Ilfeld BM, Meyer RS, Le LT, Mariano ER, Williams BA, Vandenborne K, et al. Health-related quality of life after tricompartment knee arthroplasty with and without an extended-duration continuous femoral nerve block: a prospective, 1-year follow-up of a randomized, triple-masked, placebo-controlled study. Anesth Analg. 2009 Apr; 108(4):1320–5. [PubMed: 19299806]
90. Eisenach JC. Preventing chronic pain after surgery: who, how, and when? Reg Anesth Pain Med. 2006 Jan-Feb;31(1):1–3. [PubMed: 16418016]
91. Richman JM, Liu SS, Courpas G, Wong R, Rowlingson AJ, McGready J, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg. 2006 Jan; 102(1):248–57. [PubMed: 16368838]
92. Nikolajsen L, Ilkjaer S, Christensen JH, Kroner K, Jensen TS. Randomised trial of epidural bupivacaine and morphine in prevention of stump and phantom pain in lower-limb amputation. Lancet. 1997 Nov 8; 350(9088):1353–7. [PubMed: 9365449]
93. Hayes C, Armstrong-Brown A, Burstal R. Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: a randomized, controlled trial. Anaesthesia and intensive care. 2004 Jun; 32(3):330–8. [PubMed: 15264726]
94. Elizaga AM, Smith DG, Sharar SR, Edwards WT, Hansen ST Jr. Continuous regional analgesia by intraneural block: effect on postoperative opioid requirements and phantom limb pain following amputation. J Rehabil Res Dev. 1994 Aug; 31(3):179–87. [PubMed: 7965876]
95. Ypsilantis E, Tang TY. Pre-emptive analgesia for chronic limb pain after amputation for peripheral vascular disease: a systematic review. Ann Vasc Surg. 2010 Nov; 24(8):1139–46. [PubMed: 20800987]
96. Joshi GP, Bonnet F, Shah R, Wilkinson RC, Camu F, Fischer B, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesthesia and analgesia. 2008; 107(3):1026–40. [PubMed: 18713924]
97. Lee YS, Kim H, Wu TX, Wang XM, Dionne RA. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther. 2006 May; 79(5): 407–18. [PubMed: 16678543]

$watermark-text

$watermark-text

$watermark-text

98. Hammer P, Banck MS, Amberg R, Wang C, Petznick G, Luo S, et al. mRNA-seq with agnostic splice site discovery for nervous system transcriptomics tested in chronic pain. Genome Res. 2010 Jun; 20(6):847–60. [PubMed: 20452967]

99. Hashimoto K, Oreffo RO, Gibson MB, Goldring MB, Roach HI. DNA demethylation at specific CpG sites in the IL1B promoter in response to inflammatory cytokines in human articular chondrocytes. Arthritis and rheumatism. 2009 Nov; 60(11):3303–13. [PubMed: 19877066]

100. Su RC, Becker AB, Kozyrskyj AL, Hayglass KT. Epigenetic regulation of established human type 1 versus type 2 cytokine responses. J Allergy Clin Immunol. 2008 Jan; 121(1):57–63. e3. [PubMed: 17980413]

101. Schlaghecke R, Kornely E, Wollenhaupt J, Specker C. Glucocorticoid receptors in rheumatoid arthritis. Arthritis and rheumatism. 1992 Jul; 35(7):740–4. [PubMed: 1622411]

102. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin-6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. Psychoneuroendocrinology. 2011 Oct 13.

103. Turner JD, Pelascini LP, Macedo JA, Muller CP. Highly individual methylation patterns of alternative glucocorticoid receptor promoters suggest individualized epigenetic regulatory mechanisms. Nucleic Acids Res. 2008 Dec; 36(22):7207–18. [PubMed: 19004867]

104. Zhang Z, Cai YQ, Zou F, Bie B, Pan ZZ. Epigenetic suppression of GAD65 expression mediates persistent pain. Nat Med. 2011 Oct 9.

105. Viet CT, Ye Y, Dang D, Lam DK, Achdjian S, Zhang J, et al. Re-expression of the methylated EDNRB gene in oral squamous cell carcinoma attenuates cancer-induced pain. Pain. 2011 Oct; 152(10):2323–32. [PubMed: 21782343]

106. Goh L, Samanta A. A systematic MEDLINE analysis of therapeutic approaches in ankylosing spondylitis. Rheumatol Int. 2009 Aug; 29(10):1123–35. [PubMed: 19562344]

107. Reed MR, Taylor AL. Tumour necrosis factor inhibitors in ankylosing spondylitis. Intern Med J. 2008 Oct; 38(10):781–9. [PubMed: 18422565]

108. Sommer C, Schafers M, Marziniak M, Toyka KV. Etanercept reduces hyperalgesia in experimental painful neuropathy. J Peripher Nerv Syst. 2001 Jun; 6(2):67–72. [PubMed: 11446385]

109. Dogrul A, Gul H, Yesilyurt O, Ulas UH, Yildiz O. Systemic and spinal administration of etanercept, a tumor necrosis factor alpha inhibitor, blocks tactile allodynia in diabetic mice. Acta Diabetol. 2011 Jun; 48(2):135–42. [PubMed: 21104419]

110. Kleinschnitz C, Hofstetter HH, Meuth SG, Braeuninger S, Sommer C, Stoll G. T cell infiltration after chronic constriction injury of mouse sciatic nerve is associated with interleukin-17 expression. Exp Neurol. 2006 Aug; 200(2):480–5. [PubMed: 16674943]

111. Ribeiro RA, Vale ML, Thomazzi SM, Paschoalato AB, Poole S, Ferreira SH, et al. Involvement of resident macrophages and mast cells in the writhing nociceptive response induced by zymosan and acetic acid in mice. Eur J Pharmacol. 2000 Jan 3; 387(1):111–8. [PubMed: 10633169]

112. Barclay J, Clark AK, Ganju P, Gentry C, Patel S, Wotherspoon G, et al. Role of the cysteine protease cathepsin S in neuropathic hyperalgesia. Pain. 2007 Aug; 130(3):225–34. [PubMed: 17250968]

113. Ting E, Guerrero AT, Cunha TM, Verri WA Jr, Taylor SM, Woodruff TM, et al. Role of complement C5a in mechanical inflammatory hypernociception: potential use of C5a receptor antagonists to control inflammatory pain. Br J Pharmacol. 2008 Mar; 153(5):1043–53. [PubMed: 18084313]

114. Yun JM, Jialal I, Devaraj S. Epigenetic regulation of high glucose-induced proinflammatory cytokine production in monocytes by curcumin. J Nutr Biochem. 2011 May; 22(5):450–8. [PubMed: 20655188]

115. Ke J, Long X, Liu Y, Zhang YF, Li J, Fang W, et al. Role of NF-kappaB in TNF-alpha-induced COX-2 expression in synovial fibroblasts from human TMJ. J Dent Res. 2007 Apr; 86(4):363–7. [PubMed: 17384033]

116. Ito K, Lim S, Caramori G, Chung KF, Barnes PJ, Adcock IM. Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. FASEB J. 2001 Apr; 15(6):1110–2. [PubMed: 11292684]

$watermark-text

$watermark-text

$watermark-text

117. Kiernan R, Bres V, Ng RW, Coudart MP, El Messaoudi S, Sardet C, et al. Post-activation turn-off of NF-kappa B-dependent transcription is regulated by acetylation of p65. The Journal of biological chemistry. 2003 Jan 24; 278(4):2758–66. [PubMed: 12419806]

118. Kirillov A, Kistler B, Mostoslavsky R, Cedar H, Wirth T, Bergman Y. A role for nuclear NF-kappaB in B-cell-specific demethylation of the Igkappa locus. Nat Genet. 1996 Aug; 13(4):435–41. [PubMed: 8696338]

119. Imagawa K, de Andres MC, Hashimoto K, Pitt D, Itoi E, Goldring MB, et al. The epigenetic effect of glucosamine and a nuclear factor-kappa B (NF-kB) inhibitor on primary human chondrocytes--implications for osteoarthritis. Biochem Biophys Res Commun. 2011 Feb 18; 405(3):362–7. [PubMed: 21219853]

120. Kaltschmidt B, Kaltschmidt C. NF-kappaB in the nervous system. Cold Spring Harb Perspect Biol. 2009 Sep.1(3):a001271. [PubMed: 20066105]

121. Fu ES, Zhang YP, Sagen J, Candiotti KA, Morton PD, Liebl DJ, et al. Transgenic inhibition of glial NF-kappa B reduces pain behavior and inflammation after peripheral nerve injury. Pain. 2010 Mar; 148(3):509–18. [PubMed: 20097004]

122. Montagna P. The primary headaches: genetics, epigenetics and a behavioural genetic model. J Headache Pain. 2008 Apr; 9(2):57–69. [PubMed: 18345478]

123. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000 Feb; 21(1):55–89. [PubMed: 10696570]

124. Chen P, Jiang T, Ouyang J, Cui Y, Chen Y. Epigenetic programming of diverse glucocorticoid response and inflammatory/immune-mediated disease. Med Hypotheses. 2009 Nov; 73(5):657–8. [PubMed: 19726136]

125. Vanderbilt JN, Miesfeld R, Maler BA, Yamamoto KR. Intracellular receptor concentration limits glucocorticoid-dependent enhancer activity. Mol Endocrinol. 1987 Jan; 1(1):68–74. [PubMed: 2842660]

126. Hearing SD, Norman M, Smyth C, Foy C, Dayan CM. Wide variation in lymphocyte steroid sensitivity among healthy human volunteers. J Clin Endocrinol Metab. 1999 Nov; 84(11):4149–54. [PubMed: 10566664]

127. Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr. 2007 Jun; 97(6):1064–73. [PubMed: 17433129]

128. Meaney MJ. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annu Rev Neurosci. 2001; 24:1161–92. [Review]. [PubMed: 11520931]

129. Rivarola MA, Suarez MM. Early maternal separation and chronic variable stress in adulthood changes the neural activity and the expression of glucocorticoid receptor in limbic structures. Int J Dev Neurosci. 2009 Oct; 27(6):567–74. [PubMed: 19563881]

130. Uys JD, Muller CJ, Marais L, Harvey BH, Stein DJ, Daniels WM. Early life trauma decreases glucocorticoid receptors in rat dentate gyrus upon adult re-stress: reversal by escitalopram. Neuroscience. 2006; 137(2):619–25. [PubMed: 16310967]

131. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009 Mar; 12(3):342–8. [PubMed: 19234457]

132. Diorio J, Meaney MJ. Maternal programming of defensive responses through sustained effects on gene expression. J Psychiatry Neurosci. 2007 Jul; 32(4):275–84. [PubMed: 17653296]

133. Miller G, Chen E. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. Psychosom Med. 2007 Jun; 69(5):402–9. [PubMed: 17556642]

134. van Everdingen AA, Huisman AM, Wenting MJ, van Reesema S, Jacobs JW, Bijlsma JW. Down regulation of glucocorticoid receptors in early-diagnosed rheumatoid arthritis. Clin Exp Rheumatol. 2002 Jul-Aug;20(4):463–8. [PubMed: 12175100]

$watermark-text

$watermark-text

$watermark-text

135. Lentjes EG, Griep EN, Boersma JW, Romijn FP, de Kloet ER. Glucocorticoid receptors, fibromyalgia and low back pain. Psychoneuroendocrinology. 1997 Nov; 22(8):603–14. [PubMed: 9483705]

136. Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. Science. 1999 Nov 5; 286(5442):1155–8. [PubMed: 10550053]

137. Hwang CK, Song KY, Kim CS, Choi HS, Guo XH, Law PY, et al. Evidence of endogenous mu opioid receptor regulation by epigenetic control of the promoters. Mol Cell Biol. 2007 Jul; 27(13):4720–36. [PubMed: 17452465]

138. Lim G, Wang S, Zeng Q, Sung B, Mao J. Spinal glucocorticoid receptors contribute to the development of morphine tolerance in rats. Anesthesiology. 2005 Apr; 102(4):832–7. [PubMed: 15791114]

139. Wang S, Lim G, Zeng Q, Sung B, Ai Y, Guo G, et al. Expression of central glucocorticoid receptors after peripheral nerve injury contributes to neuropathic pain behaviors in rats. J Neurosci. 2004 Sep 29; 24(39):8595–605. [PubMed: 15456833]

140. Low LA, Schweinhardt P. Early life adversity as a risk factor for fibromyalgia in later life. Pain Res Treat. 2012; 2012:140832. [PubMed: 22110940]

141. Miranda A. Early life stress and pain: an important link to functional bowel disorders. Pediatr Ann. 2009 May; 38(5):279–82. [PubMed: 19476301]

142. Davis DA, Luecken LJ, Zautra AJ. Are reports of childhood abuse related to the experience of chronic pain in adulthood? A meta-analytic review of the literature. The Clinical journal of pain. 2005 Sep-Oct;21(5):398–405. [PubMed: 16093745]

143. Green PG, Chen X, Alvarez P, Ferrari LF, Levine JD. Early-life stress produces muscle hyperalgesia and nociceptor sensitization in the adult rat. Pain. 2011 Nov; 152(11):2549–56. [PubMed: 21864980]

144. Lotsch J, Geisslinger G, Tegeder I. Genetic modulation of the pharmacological treatment of pain. Pharmacol Ther. 2009 Nov; 124(2):168–84. [PubMed: 19615406]

145. Ishizawar D, Yancy C. Racial differences in heart failure therapeutics. Heart Fail Clin. 2010 Jan; 6(1):65–74. [PubMed: 19945062]

146. Sadowska AM, Nowe V, Janssens A, Boeykens E, De Backer WA, Germonpre PR. Customizing systemic therapy in patients with advanced non-small cell lung cancer. Ther Adv Med Oncol. 2011 Jul; 3(4):207–18. [PubMed: 21904581]

147. Weitzel JN, Blazer KR, Macdonald DJ, Culver JO, Offit K. Genetics, genomics, and cancer risk assessment: State of the Art and Future Directions in the Era of Personalized Medicine. CA Cancer J Clin. 2011 Aug 19.

148. Rodriguez-Menendez V, Tremolizzo L, Cavaletti G. Targeting cancer and neuropathy with histone deacetylase inhibitors: two birds with one stone? Curr Cancer Drug Targets. 2008 Jun; 8(4):266–74. [PubMed: 18537550]

149. Sowa Y, Orita T, Minamikawa S, Nakano K, Mizuno T, Nomura H, et al. Histone deacetylase inhibitor activates the WAF1/Cip1 gene promoter through the Sp1 sites. Biochemical and biophysical research communications. 1997 Dec 8; 241(1):142–50. [PubMed: 9405248]

150. Prince HM, Bishton MJ, Harrison SJ. Clinical studies of histone deacetylase inhibitors. Clin Cancer Res. 2009 Jun 15; 15(12):3958–69. [PubMed: 19509172]

151. Szyf M. Epigenetics, DNA methylation, and chromatin modifying drugs. Annu Rev Pharmacol Toxicol. 2009; 49:243–63. [PubMed: 18851683]

152. Duvic M, Vu J. Vorinostat: a new oral histone deacetylase inhibitor approved for cutaneous T-cell lymphoma. Expert Opin Investig Drugs. 2007 Jul; 16(7):1111–20.

153. Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH. Recovery of learning and memory is associated with chromatin remodelling. Nature. 2007 May 10; 447(7141):178–82. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. [PubMed: 17468743]

154. Chiechio S, Zammataro M, Morales ME, Busceti CL, Drago F, Gereau RWt, et al. Epigenetic modulation of mGlu2 receptors by histone deacetylase inhibitors in the treatment of inflammatory pain. Mol Pharmacol. 2009 May; 75(5):1014–20. [PubMed: 19255242]

$watermark-text

155. Chung YL, Lee MY, Wang AJ, Yao LF. A therapeutic strategy uses histone deacetylase inhibitors to modulate the expression of genes involved in the pathogenesis of rheumatoid arthritis. Mol Ther. 2003 Nov; 8(5):707–17. [PubMed: 14599803]

156. Leoni F, Zaliani A, Bertolini G, Porro G, Pagani P, Pozzi P, et al. The antitumor histone deacetylase inhibitor suberoylanilide hydroxamic acid exhibits antiinflammatory properties via suppression of cytokines. Proc Natl Acad Sci U S A. 2002 Mar 5; 99(5):2995–3000. [PubMed: 11867742]

157. Lu Y, Nie J, Liu X, Zheng Y, Guo SW. Trichostatin A, a histone deacetylase inhibitor, reduces lesion growth and hyperalgesia in experimentally induced endometriosis in mice. Hum Reprod. 2010 Apr; 25(4):1014–25. [PubMed: 20118114]

158. Jones CK, Eberle EL, Peters SC, Monn JA, Shannon HE. Analgesic effects of the selective group II (mGlu2/3) metabotropic glutamate receptor agonists LY379268 and LY389795 in persistent and inflammatory pain models after acute and repeated dosing. Neuropharmacology. 2005; 49(Suppl 1):206–18. [PubMed: 15998527]

159. Lin YC, Flock KE, Cook RJ, Hunkele AJ, Loh HH, Ko JL. Effects of trichostatin A on neuronal mu-opioid receptor gene expression. Brain Res. 2008 Dec 30.1246:1–10. [PubMed: 18950606]

160. Vojinovic J, Damjanov N, D'Urzo C, Furlan A, Susic G, Pasic S, et al. Safety and efficacy of an oral histone deacetylase inhibitor in systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2011 May; 63(5):1452–8. [PubMed: 21538322]

161. Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS. Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. The Journal of biological chemistry. 2001 Sep 28; 276(39):36734–41. [PubMed: 11473107]

162. Bai G, Wei D, Zou S, Ren K, Dubner R. Inhibition of class II histone deacetylases in the spinal cord attenuates inflammatory hyperalgesia. Mol Pain. 2010; 6:51. [PubMed: 20822541]

163. Agrawal RP, Goswami J, Jain S, Kochar DK. Management of diabetic neuropathy by sodium valproate and glyceryl trinitrate spray: a prospective double-blind randomized placebo-controlled study. Diabetes Res Clin Pract. 2009 Mar; 83(3):371–8. [PubMed: 19208440]

164. Freitag FG, Diamond S, Diamond ML, Urban GJ. Divalproex in the long-term treatment of chronic daily headache. Headache. 2001 Mar; 41(3):271–8. [PubMed: 11264687]

165. Capuano A, Vollono C, Mei D, Pierguidi L, Ferraro D, Di Trapani G. Antiepileptic drugs in migraine prophylaxis: state of the art. Clin Ter. 2004 Feb-Mar;155(2–3):79–87. [PubMed: 15244112]

166. Chiba T, Yokosuka O, Arai M, Tada M, Fukai K, Imazeki F, et al. Identification of genes up-regulated by histone deacetylase inhibition with cDNA microarray and exploration of epigenetic alterations on hepatoma cells. Journal of hepatology. 2004 Sep; 41(3):436–45. [PubMed: 15336447]

167. Lee HS, Park MH, Yang SJ, Jung HY, Byun SS, Lee DS, et al. Gene expression analysis in human gastric cancer cell line treated with trichostatin A and S-adenosyl-L-homocysteine using cDNA microarray. Biol Pharm Bull. 2004 Oct; 27(10):1497–503. [PubMed: 15467184]

168. Rajan I, Savelieva KV, Ye GL, Wang CY, Malbari MM, Friddle C, et al. Loss of the putative catalytic domain of HDAC4 leads to reduced thermal nociception and seizures while allowing normal bone development. PLoS One. 2009; 4(8):e6612. [PubMed: 19672313]

169. Black C, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, et al. The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. Health Technol Assess. 2009 Nov; 13(52):1–148. [Review]. [PubMed: 19903416]

170. Largo R, Alvarez-Soria MA, Diez-Ortego I, Calvo E, Sanchez-Pernaute O, Egido J, et al. Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. Osteoarthritis Cartilage. 2003 Apr; 11(4):290–8. [PubMed: 12681956]

171. Detich N, Bovenzi V, Szyf M. Valproate induces replication-independent active DNA demethylation. The Journal of biological chemistry. 2003 Jul 25; 278(30):27586–92. [PubMed: 12748177]

$watermark-text

172. Dong E, Guidotti A, Grayson DR, Costa E. Histone hyperacetylation induces demethylation of reelin and 67-kDa glutamic acid decarboxylase promoters. Proc Natl Acad Sci U S A. 2007 Mar 13; 104(11):4676–81. [PubMed: 17360583]

173. Villeda SA, Akopians AL, Babayan AH, Basbaum AI, Phelps PE. Absence of Reelin results in altered nociception and aberrant neuronal positioning in the dorsal spinal cord. Neuroscience. 2006; 139(4):1385–96. [PubMed: 16580148]

174. Chen Y, Beffert U, Ertunc M, Tang TS, Kavalali ET, Bezprozvanny I, et al. Reelin modulates NMDA receptor activity in cortical neurons. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2005 Sep 7; 25(36):8209–16. [PubMed: 16148228]

175. Mitchell CP, Chen Y, Kundakovic M, Costa E, Grayson DR. Histone deacetylase inhibitors decrease reelin promoter methylation in vitro. J Neurochem. 2005 Apr; 93(2):483–92. [PubMed: 15816871]

176. Weaver IC, Champagne FA, Brown SE, Dymov S, Sharma S, Meaney MJ, et al. Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. J Neurosci. 2005 Nov 23; 25(47):11045–54. [PubMed: 16306417]

177. Cooney CA, Dave AA, Wolff GL. Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring. J Nutr. 2002 Aug; 132(8 Suppl):2393S–400S. [PubMed: 12163699]

178. Waterhouse PM, Wang MB, Lough T. Gene silencing as an adaptive defence against viruses. Nature. 2001 Jun 14; 411(6839):834–42. [Review]. [PubMed: 11459066]

179. McCaffrey AP, Meuse L, Pham TT, Conklin DS, Hannon GJ, Kay MA. RNA interference in adult mice. Nature. 2002 Jul 4; 418(6893):38–9. [PubMed: 12097900]

180. Tan PH, Yang LC, Shih HC, Lan KC, Cheng JT. Gene knockdown with intrathecal siRNA of NMDA receptor NR2B subunit reduces formalin-induced nociception in the rat. Gene Ther. 2005 Jan; 12(1):59–66. [PubMed: 15470478]

181. Garraway SM, Xu Q, Inturrisi CE. Design and evaluation of small interfering RNAs that target expression of the N-methyl-D-aspartate receptor NR1 subunit gene in the spinal cord dorsal horn. J Pharmacol Exp Ther. 2007 Sep; 322(3):982–8. [PubMed: 17551091]

182. Kasama S, Kawakubo M, Suzuki T, Nishizawa T, Ishida A, Nakayama J. RNA interference-mediated knock-down of transient receptor potential vanilloid 1 prevents forepaw inflammatory hyperalgesia in rat. Eur J Neurosci. 2007 May; 25(10):2956–63. [PubMed: 17509082]

183. Guo W, Robbins MT, Wei F, Zou S, Dubner R, Ren K. Supraspinal brain-derived neurotrophic factor signaling: a novel mechanism for descending pain facilitation. J Neurosci. 2006 Jan 4; 26(1):126–37. [PubMed: 16399679]

184. Sorensen DR, Leirdal M, Sioud M. Gene silencing by systemic delivery of synthetic siRNAs in adult mice. J Mol Biol. 2003 Apr 4; 327(4):761–6. [PubMed: 12654261]

$watermark-text
$watermark-text
$watermark-text

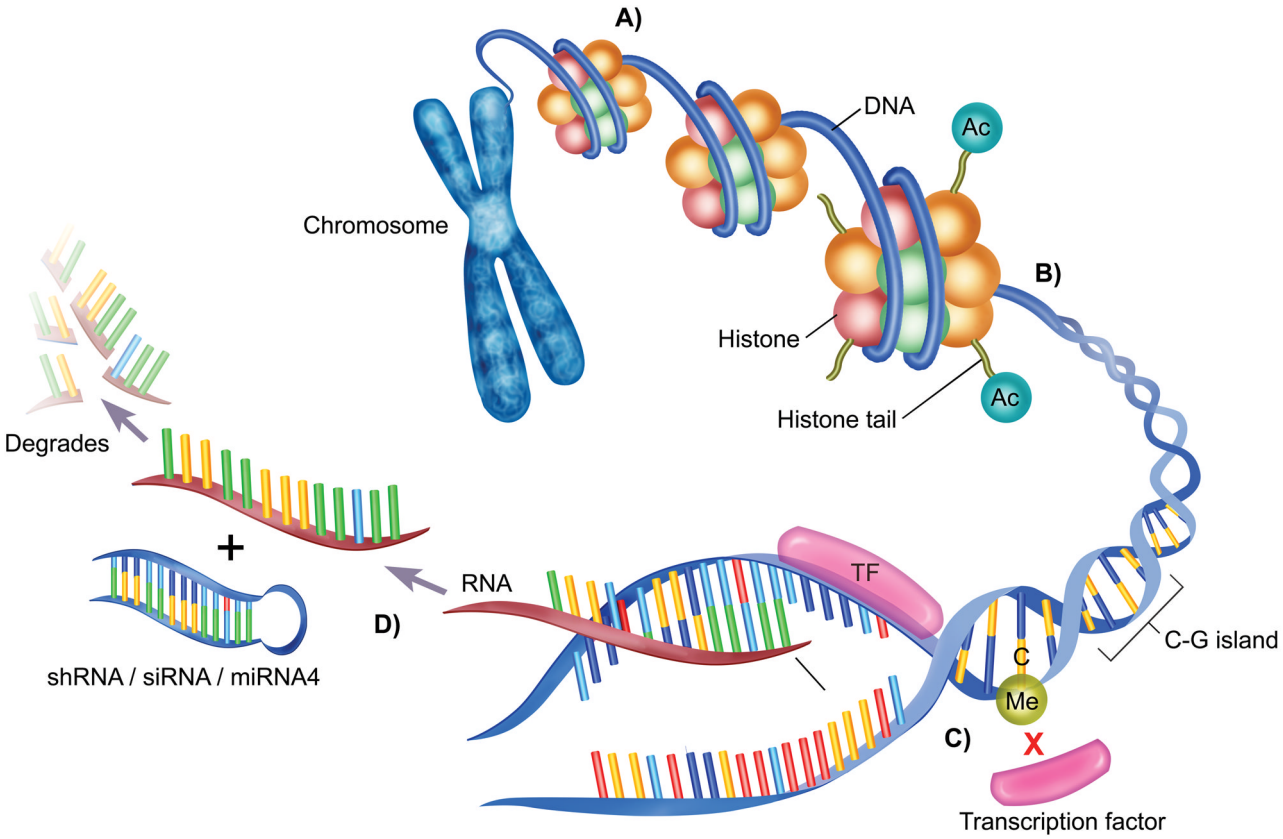

Figure 1. Epigenetic Mechanisms

A) DNA wraps around histone octamers to form a nucleosome, the fundamental building block of chromatin. B) Histone proteins may be modified through several processes, including acetylation. The addition of an acetyl group to histone tails generally opens the chromatin structure and facilitates transcription factor binding, enhancing gene expression. C) Methylation of cytosine nucleotides in C-G rich sequences (“CG Islands”) prevents the binding of transcription factors and generally silences gene expression. These CG Islands are often found near promoter regions and serve a significant role in gene regulation. D) Post-transcriptional regulatory mechanisms include short hairpin RNA (shRNA), small interfering RNA, (siRNA) and micro RNA (miRNA) that bind RNA and induce their degradation.

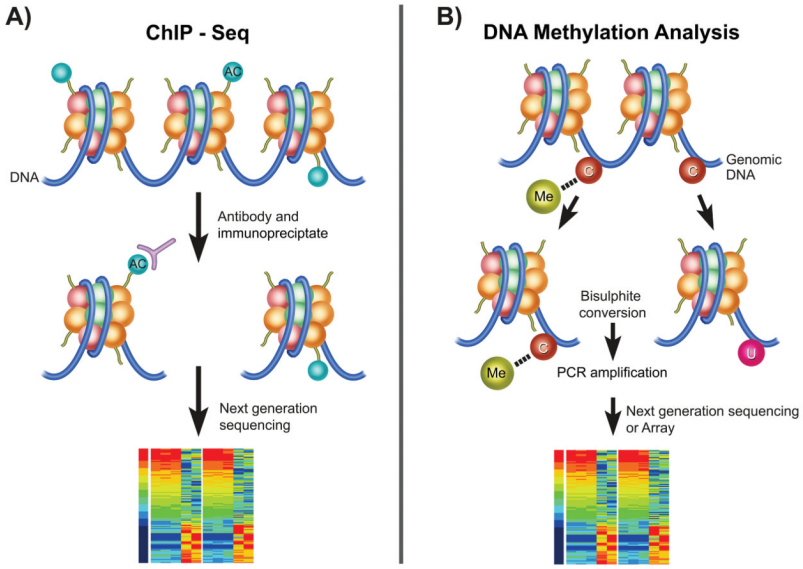

Figure 2. Laboratory Techniques in Epigenetics

A) In ChIP-Seq analysis, an antibody is used on chromatin to immunoprecipitate and select for acetylation and other histone modifications. The results may then be analyzed through several techniques including genome-wide next generation sequencing. In this manner, the histone acetylation patterns of a particular tissue may be determined. B) The analysis of DNA methylation employs bisulfite sequencing to convert unmethylated cytosines to uracil. This process does not affect the methylated cytosines. The methylation patterns can be calculated by comparing the ratio of cytosine to uracil.

$watermark-text
$watermark-text
$watermark-text

$watermark-text

$watermark-text

$watermark-text

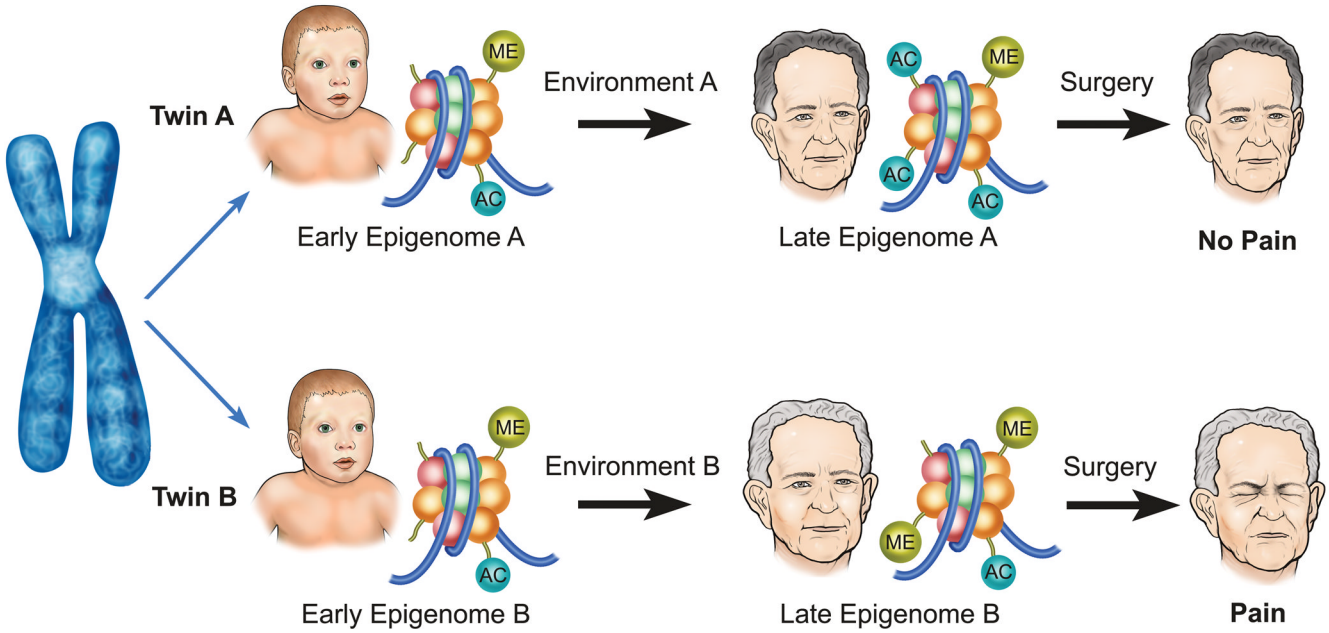

Figure 3. Epigenome and Chronic Pain

Twin A and Twin B demonstrate similar "epigenomes" at birth with few (if any) differences in methylation and acetylation patterns. Environmental factors throughout development affect histone acetylation patterns and cytosine methylation patterns, resulting in phenotypic differences by adulthood. With surgery or nerve injury, these epigenetic differences may result in differing risks of chronic pain.

$watermark-text

$watermark-text

$watermark-text

Table 1

Epigenetically Active Drugs and their Mechanisms

Epigenetics Mechanism	Drug	Action	Clinical Use	Comments
Histone Deacetylase Inhibitor	Valproic Acid	Inhibits Class I and II HDAC	Seizures, Pain	Effective for migraine prophylaxis
	Givinostat	Inhibits Class I and II HDAC	Juvenile idiopathic arthritis	Effective in human arthritis trial
	Tricostatin A (TSA)	Inhibits Class I and II HDAC	Laboratory only	Produces analgesia in animal models. Enhances μ-opioid receptor transcription
	Suberoylanilide hydroxamic acid (SAHA)	Inhibits Class I HDAC	Laboratory only	Produces analgesia in animal models
DNA Methylation	Glucosamine	Prevents demethylation of IL-1β gene promoter	Arthritis pain	Common clinical use. Effect on IL-1β reduces inflammatory cytokine production
	Valproic Acid	Induces demethylation of Reelin promoter	Seizures, Pain	Reelin modulates NMDA function and pain processing
	L-methionine	Induces methylation at glucocorticoid receptor promoter gene	Dietary Supplement	Alters experimental stress response. Used as dietary supplement for arthritis
RNA Interference	SiRNA targeted to NMDA receptor subunits	Gene silencing of NR1 and NR2 subunits of NMDA	Experimental	Produces analgesia in animal models
	SiRNA to P2X3	Gene silencing of P2X3	Experimental	Produces analgesia in animal models. No observed neurotoxicity with intrathecal use.
	SiRNA to TNF-α	Gene silencing of TNF-α	Experimental	Produces analgesia in animal models