Prescription Opioid Misuse

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Contributor: Maria Carla Gerra

Prescription opioids are used for some chronic pain conditions. However, generally, long-term therapy has unwanted side effects which may trigger addiction, overdose, and eventually cause deaths. Opioid addiction and chronic pain conditions have both been associated with evidence of genetic and epigenetic alterations. Despite intense research interest, many questions about the contribution of epigenetic changes to this typology of addiction vulnerability and development remain unanswered.

Keywords: epigenetics ; prescription opioids ; pain

1. Introduction

Chronic pain represents significant public health concerns and prescription opioids are a common treatment option for cancer pain management, for end-of-life treatment, in relation to surgery, and for short-term use in severe acute/chronic pain conditions not related to cancer [1]. The non-medical use of opioids and their negative health consequences among people who use drugs have been studied since 2007 after the spread of the opioid crisis. However, in the last few years, we have witnessed a new opioid crisis, even among young people and categories of workers, particularly in North America, the Middle East, Asia, and Africa. This crisis is related to the non-medical use of prescription opioids that can result in opioid misuse, defined as “use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects” [2]. Signs of an increase in methadone, buprenorphine, fentanyl, codeine, morphine, tramadol, and oxycodone misuse and the increased prescription rates for opioids for pain management have also been observed in Europe resulting in an increase of vulnerable cohorts of long-term opioid users [3]. The central issue is that long-term opioid therapy is associated with many side effects such as addiction, development of tolerance, and opioid-induced hyperalgesia. In addition, in 2018 more than one-third of overdose deaths involved pharmaceutical opioids with the number of overdose deaths rising from 3442 in 1999 to 17,029 in 2017 [4][5].

Opioid drugs act not only in nociceptive processes but also in modulating gastrointestinal, endocrine, and autonomic functions, as well as in affecting cognition and reward systems [6]. The relationship between pain states and substance abuse/misuse has been recently examined. Opioids carried an increased susceptibility to abuse even during initial exposure for pain treatment; in particular, when too many opioid drugs are prescribed for conditions not supposed to be treated by opioids or if healthcare systems are not set up to control the number of opioid prescriptions to an individual patient (doctor shopping) [7][8][9].

Nevertheless, it is important to note that the lack of consistent findings regarding the identification of personal risk factors that may predict opioid misuse in chronic pain patients was recently evidenced in the literature [10]. Among the possible risk factors, the individual genetic variability in conjunction with chronic pain, both affecting stress and reward systems, lead to differential responses to opioids and may determine the transition risk from therapeutic use to opioid addiction. Addiction is a multifactorial condition as both genetics and psychosocial factors can trigger opioid addictive behaviors. Polymorphisms in the *μ*-opioid receptor 1 (*OPRM1*), the cytochrome P450 2D6 (*CYP2D6*), the catechol-O-methyl transferase (*COMT*) genes and in the ATP-binding cassette family genes have been found to be associated with differences in morphine consumption and metabolization process [11]. The main environmental factors important for developing opioid/substance abuse are described as psychiatric medication prescriptions, mood disorders, specific mental health diagnoses, and adverse childhood experiences [12][13].

2. Prescription Opioids Pain Relievers

Opioid receptors are widely distributed both centrally and in the periphery, particularly in the periaqueductal grey, *locus ceruleus*, rostral ventral medulla, and in the *substantia gelatinosa* of the dorsal horn. The major mechanism through which opioids relieve pain is the stimulation of descending inhibitory neurons through activation of the μ opioid MOP receptors.

Common prescription opioids responsible for this opioid-induced analgesia effect are morphine, codeine, tramadol, fentanyl, hydromorphone, buprenorphine, hydrocodone, oxycodone, oxymorphone, methadone, and tapentadol [14].

Opioid medications are often prescribed for acute episodes of pain for short-term use or for cancer-related pain. Opioids are also used for chronic non-cancer pain in selected cases when non-opioid and adjuvant therapies have failed and other pain medications have proven ineffective. These drugs are defined as highly effective and safe analgesics when used appropriately and included in a multifaceted strategy by competent clinicians [15].

However, since opioid-induced pain relief and addiction do not act through distinct mechanisms in distinct brain areas, opioid drugs could not only have a simple analgesic effect but also affect or compromise the ability to feel pleasure and socialize as well as the reward system [16]. Neural changes were likened between chronic pain and long-term substance abuse; in fact, dysfunctional learning may trigger both these pathological states, producing an extensive reorganization in chronic pain and converting functional rewards into the craving characteristic of addiction [17].

In light of the fact that the opioid analgesic efficacy often decreases with continuous use and that patients with refractory complex chronic pain are at high risk of abuse, a two-level strategy might be set up to contrast the opioid crisis. The first level would include prescription monitoring programs and dose limitations to prevent abuse/misuse; the second could increase research at the molecular level to identify the central and peripheral mechanisms underlying the drug action and to explore precision medicine options.

3. Epigenetics and Prescription Opioids

The term epigenetics refers to the study of heritable changes in the gene function that do not involve changes in the DNA sequence [18]. Epigenetics includes three main mechanisms: DNA methylation and chromatin-related modifications, both affecting the ability of transcriptional machinery to access the DNA tightly packed into chromatin, and non-coding RNAs (ncRNAs).

DNA methylation, the addition of a methyl group on the 5th carbon of the DNA cytosine, is shown particularly relevant in CpG islands, regions of the genome containing a large number of CpG dinucleotide repeats [19]. It regulates gene expression facilitating the recruiting of proteins involved in the gene repression or inhibiting the binding of transcription factors to DNA [20]. Thus, DNA methylation plays a critical role in the regulation of gene expression. Whole-genome methylation profiling has made it possible to better explore demethylation and de novo methylation in the maternal and paternal genomes during development. This enables highlighting of more complex dynamics within the heterogeneous methylation level at CpG-rich promoters in different cell types. Many unannotated sequences and inactive transposons affected by this epigenetic mark were revealed [21]. Opioids have been demonstrated to stimulate DNA methylation. One study identified the global DNA methylation at LINE-1 as significantly correlated with increased chronic pain. Thus, it was hypothesized that opioid analgesics might be causally associated with increased genome-wide DNA methylation [22].

The chromatin modifications include those related to histone tails, such as histone methylation, chromatin remodeling, and post-translational modifications affecting electrostatic nucleosome interactions. These changes have been clinically and pre-clinically evidenced to be associated with opioid exposures [23]. Concerning prescription opioids, oxycodone exposure was shown to induce long-term epigenetic consequences in the ventral tegmental area (VTA) of the developing brain with an enrichment of the repressive histone mark, H3K27me3, in prolonged oxycodone withdrawal and with consistent inhibition of the gene regulation [24]. The other chromatin modifications are related to the chromatin structure that is hierarchically folded at different levels in the nucleus with a 3D organization [25]. Previous works evidenced a correlation between the effects of opioids and chromatin remodelers such as CREB, Sox10, and BRG1 [26][27][28]. However, no studies have thoroughly explored prescription opioids' effect on chromatin structure remodeling.

The third important regulator of transcriptional activity is represented by ncRNAs [29], i.e., RNA not translated into proteins. ncRNAs act through a variety of mechanisms such as post-transcriptional silencers or activators. Moreover, they are involved in regulating protein-coding and non-coding genes' expression, in the guide of chromatin-modifying complexes to specific genomic loci, in the modulation of transcriptional programs, and providing molecular scaffolds [30]. ncRNAs have already been correlated with opioid exposure. In particular, morphine, fentanyl, and heroin were found to modulate the expression of specific micro-RNAs [31][32]. Additional studies are required to understand the functional consequences of these epigenetic changes.

The nociceptive response was demonstrated to activate these epigenetic mechanisms by modulating pain genes and possibly mediating the transition from acute to chronic pain. Studies highlight that also opioids are involved in diverse

types of epigenetic regulation and thus they might influence the analgesic effects or the increased risk of continued opioid intake and development of a substance use disorder following long-term opioid therapy [33][34].

However, the identification of specific factors associated with the individual opioid response or with side effect vulnerability has just been launched. The molecular mechanisms through which some individuals develop negative consequences associated with prolonged prescription opioid use, including hyperalgesia, addiction, sleep problems, hypogonadism, fractures, and surgical failures [35][36] are poorly understood. The following paragraphs provide an overview of the animal and human studies investigating epigenetic changes associated with opioid therapy initiated for pain relief. The studies are illustrated in **Table 1**; **Table 2**, respectively.

Table 1. Epigenetic changes after prescribed opioid exposure in experimental models.

Opioids	Tissues/Sample	Epigenetic Methods	Change	Animals	Findings	PMID	Authors
Morphine	Brain tissues (PAG, PFC, temporal lobe, and ventral striatum)	Microarray gene expression profiling and pattern matching	Gene expression	Adult male mice	The development of tolerance is influenced by a region in *OPRM1* gene. The genes epigenetically modified by chronic morphine administration are mainly related to neuroadaptation.	19386926	Tapocik et al., 2009 [37]
Morphine	NAc	Chromatin immunoprecipitation followed by massive parallel sequencing	H3K9me2 distribution in NAc in the absence and presence of chronic morphine	9 to 11-week-old C57BL/6J male mice or G9afl/fl mice	Chronic morphine decreases G9a expression and H3K9me2 at global level and in specific loci in mouse NAc.	23197736	Sun et al., 2012 [38]
Morphine	Central nucleus of amygdala	Chromatin immunoprecipitation	Gene and protein expression	Female mice with persistent and acute pain	Persistent pain and repeated morphine upregulate the transcriptional regulator MeCP2. MeCP2 enhances *BDNF* expression and represses G9a action and its repressive mark H3K9me2 in CeA.	24990928	Zhang et al., 2014 [39]
Morphine	Central nucleus of amygdala	Chromatin immunoprecipitation	Gene expression	Rat model of morphine self-administration	The repression of GluA1 function by MeCp2 is proposed as a mechanism for morphine-seeking behavior in pain experience.	25716866	Hou et al., 2015 [40]
Morphine	Dorsal root ganglia and spinal cord tissues	Quantitative RT-PCR, Western Immunoblotting and ChIP-PCR	Gene and protein expression, histone modifications analysis	Male Sprague-Dawley rats SNL (spinal nerve ligation) model	G9a contributes to transcriptional repression of MORs in primary sensory neurons in neuropathic pain. G9a inhibitors: potential treatment of chronic neuropathic pain	26917724	Zhang et al., 2016 [41]

Opioids	Tissues/Sample	Epigenetic Methods	Change	Animals	Findings	PMID	Authors
Morphine	Dorsal root ganglia	Quantitative RT-PCR and Western Blot	Gene and protein expression	Adult male CD-1 mice	Neuropathic pain increases C/EBPβ expression. C/EPBβ activates the G9a gene, that epigenetically silences Kv1.2 and MOR genes. Blocking the induced increase in C/EBPβ in the DRG, morphine analgesia after CCI is improved.	28698219	Li et al., 2017 [42]
Morphine	Basolateral amygdala	Quantitative RT-PCR and Western Blot	Gene and protein expression	Male Sprague–Dawley	Increase in H3K14ac together with upregulation of the *BDNF* and *FosB*; and CREB activation.	24829091	Wang et al., 2015 [43]
Morphine	Rat brain regions	Pyrosequencing	DNA methylation (5mC) and global DNA 5-hydroxymethylation (5hmC)	Male Wistar rats	Acute and chronic exposure is associated with significantly decreased/increased 5mC at specific genes (*BDNF, IL1B, IL6, NR3C1, COMT*). Global 5hmC levels increase in the cerebral cortex, hippocampus, and hypothalamus, but decrease in the midbrain.	29111854	Barrow et al., 2017 [44]
Morphine, phentayl	Hippocampus	RNAseq	Gene and protein expression	Mice chronically treated with μ-opioid agonists	The increased expression of MiR-339-3p inhibits intracellular MOR biosynthesis and acts as a negative feedback modulator of MOR signals.	23085997	Wu et al., 2013 [31]
Morphine	Dorsal root ganglia	Quantitative RT-PCR and Western Blot	Gene and protein expression	Male CD-1 mice treated with morphine to establish systemic chronic tolerance to morphine anti-nociception	MiR-219 contributes to the development of chronic tolerance to morphine analgesia by targeting CaMKIIγ and enhancing CaMKIIγ-dependent brain-derived neurotrophic factor expression.	27599867	Hu et al., 2016 [45]
Morphine	Dorsal root ganglia	Quantitative RT-PCR and Western Blot	Gene and protein expression	Male CD-1 mice injected with morphine to elicit morphine tolerance	The increased *BDNF* expression is regulated by the miR-375 and JAK2/STAT3 pathway. Inhibition of this pathway decreases BDNF production, and thus, attenuated morphine tolerance.	28603428	Li et al., 2017 [46]
Oxycodone	Ventral tegmental area of the developing brain	Quantitative RT-PCR and chromatin immunoprecipitation	Gene expression and histone modifications analysis	Male offspring of C57Bl/6NTac mice	Adolescent oxycodone exposure increases the repressive mark H3K27me3, at key dopamine-related genes.	33325096	Carpenter et al., 2020 [24]

Table 2. Epigenetic changes after prescribed opioid exposure in humans.

Opioids	Tissues/Sample	Epigenetic Methods	Change	Animals	Findings	PMID	Authors
Oxycodone	Striatum (NAc and CPu)	RNAseq	Gene expression	Mice following extended 14-day oxycodone self-administration	Alterations in the expression of heterodimer receptor, integrins, semaphorins, semaphorin receptors, plexins, selective axon guidance genes.	29946272	Yuferov et al., 2018 [47]
Oxycodone	Dorsal striatum and ventral striatum	RNAseq	Gene expression	Adult male C57BL/6J mice underwent a 14-day oxycodone self-administration	Three genome-wide significant differentially methylated CpGs map to genes involved in chromatin remodeling, DNA binding, cell survival, and cell projection (*PARG*, *RERE*, and *CPAP7* genes). Inflammation/immune genes have altered expression during chronic self-administration of oxycodone	28653080	Zhang et al., 2017 [48]
Opioids	Whole blood	Bisulfite modification and Array-based genome-wide DNA methylation assay	DNA methylation at specific CpG sites	140 opioid dependence cases and 80 opioid-exposed controls		31801960	Montalvo-Ortiz et al., 2019 [51]
Oxycodone	Hippocampus	DNA ELISA Kit for total 5mC; quantitative RT-PCR	Global 5mC levels and gene expression	Male Sprague-Dawley rats	The global DNA hypomethylation induced by oxycodone can be reversed through oxytocin and could significantly attenuate the oxycodone-rewarding effects.	31526808	Fan et al., 2019 [49]
Opioid medication self-administration (hydrocodone, oxycodone, and codeine: 5–30 mg)	Saliva collected at 3 time points	Genome-wide DNA methylation assay and candidate approach	DNA methylation at *OPRM1* gene promoter	33 opioid-naïve participants who underwent standard dental surgery	Hypermethylation of the *OPRM1* promoter is measured in response to opioid use, and such epigenetic restructuring can be induced acutely by short-term use of therapeutic opioids.	32493461	Sandoval-Sierra et al., 2020 [52]
Oxycodone	Ventral tegmental area	DNA ELISA Kit for total 5mC and OneStep qMethyl™ kit for gene-specific 5mC, quantitative RT-PCR, Western blotting	Global and specific 5mC levels and gene expression	Sprague-Dawley rats	Down-regulation of DNMT1 and up-regulation of TET1-3 lead to a decrease in global 5mC levels and differential demethylation at exon 1 of *SYN* and exon 2 of *PSD95*.	31735530	Fan et al., 2019 [50]
Remifentanil, oxycodone, codeine	Whole blood	Pyrosequencing at specific CpG sites and LINE1 (global genome-wide DNA methylation assay)	DNA methylation	140 women with persistent pain after breast cancer surgery	The global DNA methylation is shown to be a pain predictive biomarker, providing useful information to allocate the patients to either a “persistent pain” or “non-persistent pain” phenotype.	31775878	Kringel et al., 2019 [53]

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