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REVIEW

The molecular neurobiology of chronic pain–induced depression

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Abstract

The increasing number of individuals with comorbidities poses an urgent need to improve the management of patients with multiple co-existing diseases. Among these comorbidities, chronic pain and mood disorders, two long-lasting disabling conditions that significantly reduce the quality of life, could be cited first. The recent development of animal models accelerated the studies focusing on the underlying mechanisms of the chronic pain and depression/anxiety comorbidity. This review provides an overview of clinical and pre-clinical studies performed over the past two decades addressing the molecular aspects of the comorbid relationship of chronic pain and depression. We thus focused on the studies that investigated the molecular characteristics of the comorbid relationship between chronic pain and mood disorders, especially major depressive disorders, from the genetic and epigenetic point of view to key neuromodulators which have been shown to play an important role in this comorbidity.

Keywords Chronic pain · Depression · Molecular characteristics · Behavior · Neuropathic pain

Introduction

Depressive disorders affect around 16% of the population at some point over their lifespan (Bromet et al. 2011) and result in personal suffering and notable economic burden (Simon 2003). They comprise disabling and long-lasting conditions, which are estimated to become foremost contributors to the worldwide burden of disease by 2030 (WHO 2008). While chronic stress is a relevant etiology (Pittenger and Duman 2008), chronic pain is also among the first determinants of mood disorders (Attal et al. 2011). Indeed, a mean prevalence rate around 50% for major depressive disorder has been reported in patients with chronic pain (Bair et al. 2003). Therefore, it is imperative to closely focus on understanding the causes and effects of the relationship of chronic pain and mood disorder in order to come up with more effective treatment strategies.

A strong asset of pre-clinical studies is the use of animal models for mimicking various aspects of chronic pain and mood disorder characteristics. The most utilized animal models of chronic pain, which will be mentioned throughout this review, are those imitating common chronic pain pathologies such as neuropathic pain, which results from lesions or disease affecting the somatosensory system, or chronic joint inflammation observed in arthritic pain, but also dysfunctional pain syndromes such as fibromyalgia and irritable bowel syndrome (IBS) (Leite-Almeida et al. 2015). Models of neuropathic pain in rodents can be based on peripheral nerve injuries, central injuries, trigeminal neuralgia, diabetic neuropathies, chemo-induced neuropathies, postherpetic neuralgia, and so forth (see reviews of Barrot 2012; Sorkin and Yaksh 2009). Almost all of the pre-clinical studies on the anxiodepressive consequences of neuropathic pain were performed on models related to sciatic nerve manipulation, using either nerve compression or section (see Table 1). Inflammatory models are based on injection of inflammatory agents such as formalin, capsaicin, carrageenan, and complete Freund's adjuvant (CFA) (Duric and McCarson 2006, 2007; Zhao et al. 2007; Li et al. 2009b; Kim et al. 2012). The most frequently used tests for assessing depression-related behaviors in rodents involve exposure to stressful situations and the measure of time spent in active versus passive stress

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Table 1 Traumatic neuropathy models used to induce chronic neuropathic pain and concomitant anxiodepressive-like behaviors

		Phenotype onset (post-op)		
Model	Behavioral test	Anxiety-like	Depressive-like	References
CCI	EPM, OF, FST, SPT, TST	2–4 weeks	2–6 weeks	Caspani et al. 2014; Roeska et al. 2008; Li et al. 2014; Urban et al. 2011; Gregoire et al. 2012; Hu et al. 2009; Fukuhara et al. 2012; Alba-Delgado et al. 2013; Zhao et al. 2014a, b; Zeng et al. 2008; Dellarole et al. 2014
PSNL	EPM, OF, DLB, FST, SPT, TST	2–4 weeks	4 weeks	Narita et al. 2006a, b; Matsuzawa-Yanagida et al. 2007; Roeska et al. 2008; Sawada et al. 2014; Wallace et al. 2007; Bura et al. 2013; Gai et al. 2014
SNC	EPM, OF, DLB, FST, SPT, NSF	4–6 weeks	6–9 weeks	Benbouzid et al. 2008; Yalcin et al. 2011; Dimitrov et al. 2014
SCI	OF, SPT, TST	No phenotype at 4–7 weeks	8 weeks	Galan-Arriero et al. 2014; Wu et al. 2014
SNI	EPM, OF, DLB, FST, SPT	3–4 weeks	1–2 weeks	Leite-Almeida et al. 2009, 2012; Urban et al. 2011; Mutso et al. 2012; Avila-Martin et al. 2015; Gonçalves et al. 2008; Norman et al. 2010b; Goffer et al. 2013; Stratinaki et al. 2013
SNL	EPM, OF, DLB, FST	2–4 weeks	4–8 weeks	Suzuki et al. 2007
SNT	OF, FST	4 weeks	4 weeks	Hu et al. 2010; Hasnie et al. 2007

CCI, chronic constriction injury; *PSNL*, partial sciatic nerve ligation; SNC, sciatic nerve cuffing; *SCI*, spinal cord injury; *SNI*, spared nerve injury; *SNL*, spinal nerve ligation; *SNT*, spinal nerve transection; *DLB*, dark-light box; *EPM*, elevated plus-maze; *FST*, forced swimming test; *NSF*, novelty suppressed feeding; *OF*, open field; *SPT*, sucrose preference test; *TST*, tail suspension test

coping, such as the forced swimming test or the tail suspension test. Another symptom, frequently examined, is the animal's interest in pleasurable activities such as the preference for sucrose solution or engaging in social interactions (see reviews of Yalcin et al. 2014; Leite-Almeida et al. 2015). Since the late 1990s, several research groups worked on modeling the anxiodepressive consequences of chronic pain in animals. The first studies (Kontinen et al. 1999) and some recent ones (Kodama et al. 2011; Urban et al. 2011; Pitzer et al. 2019) failed to show the comorbidity of chronic pain and depression, while other studies reported anxiety and/or depressive-like consequences in rodent models (see review of Yalcin et al. 2014). Temporal parameter (time after the surgery), species, strains of animals, chronic pain models, and the time of the day-night cycle when the animals are tested may all influence the results.

Hence, this review summarizes a portion of clinical and pre-clinical research performed over the past two decades pertaining to molecular aspects of the comorbid relationship of chronic pain and depression. The main hypothesis is that the close reciprocal relationship of these two pathologies can be due to common underlying biological mechanisms linking these pathologies (Liu and Chen 2014). We thus focused on the studies that investigated the molecular characteristics of the comorbid relationship between chronic pain and mood disorders, especially major depressive disorders, from the genetic and epigenetic point of view to key neuromodulators which have been shown to play an important role in this comorbidity.

The contribution of genetic and epigenetic modifications

Genetic modifications

In the past decades, several studies highlighted the individual differences in response to chronic pain and susceptibility to mood disorders which suggest that genetic factors play a significant role in the comorbidity of pain and depression (Magni et al. 1987; Reichborn-Kjennerud et al. 2002; Lembo et al. 2007; McIntosh et al. 2016). A common approach to study the effect of genetics on physical and mental conditions is by looking at monozygotic and dizygotic twins, who share 100% and 50% of their genes, respectively. A study by Lembo et al. (2007) looked at a total of 986 twin pairs and found that there is a genetic contribution to chronic pain associated with IBS, which may be mediated by the hereditability of anxiety and depression. Indeed, they estimated 22% of genetic variance for IBS which became non-significant when adjusted for anxiety and depression, suggesting that mood disorders such as depression and chronic pain disorders possibly follow a similar causal genetic pathway. Similarly, Pinheiro et al. (2018) found that 64% of genetic factors covariate between chronic low back pain and symptoms of depression and anxiety, supporting a potential role of common biological pathways.

Besides studies suggesting that common genetic factors might mediate the heritability of chronic pain and depression (Reyes-Gibby et al. 2013; Burri et al. 2015; Pinheiro et al. 2015; Gasperi et al. 2017), there is also evidence that environmental factors such as early shared environment or sleep quality might also play a substantial role in the vulnerability to chronic pain and mood disorders (Pinheiro et al. 2015; Gasperi et al. 2017). Interestingly, McIntosh et al. (2016) showed that presence of chronic pain and genetic predisposition in a spouse has a significant contribution to their partner's risk of developing a comorbidity of chronic pain and mood disorders. It is also intriguing that patients who suffer from chronic pain generally have more first-degree relatives who suffer from depression compared to general population, even if they personally do not have a history of depression (Lepine and Briley 2004; Magni et al. 1987).

However, besides heritability studies, which use statistics to estimates the degree of variation in a phenotypic trait due to genetics, there are many other which took a more in-depth approach and looked at single-nucleotide polymorphisms (SNPs) of specific genes in order to further delineate the comorbidity of chronic pain and mood disorders (Lee et al. 2012). Some of the extensively studied polymorphisms are those of the brain-derived neurotrophic factor (BDNF), which is the most widespread neurotrophin in the central nervous system (CNS) (Hofer et al. 1990) and also highly abundant in non-neuronal cells and tissues such as platelets and blood vessels (Donovan et al. 2000). In particular, the BDNF Val66Met SNP seems to be closely related to the pain-depression comorbidity since it has been shown to moderate the relationship between life stress and depression (Hosang et al. 2014), life stress and chronic multi-site musculoskeletal pain (Generaal et al. 2016), and coronary artery disease and depression (Bozzini et al. 2009). Other frequent targets of SNP studies are receptors of various ligands which play a role in the relationship of pain and depression. For instance, although inconclusive, Max et al. (2006) showed that the galanin-2 receptors are potential candidates to mediate the affective consequences of pain, since two of its allele copies show a pain-gene interaction and are associated with post-surgical mood disorder protection. Moreover, Lebe et al. (2013) found that women, but not men, harboring the promoter polymorphisms of serotonin receptor-1A (5HTR1A) and serotonin receptor-2A (5HTR2A) showed significantly higher depression scores due to chronic pain. Taken together, these studies highlight the pivotal role of genetic variations (see Table 2) in the development of chronic pain and mood disorders and point to the need of further understanding how individual genetic characteristics shape the comorbid relationship of pain and depression.

Epigenetic modifications

Epigenetic mechanisms characterized by structural chromatin modifications that allow or prevent transcription factors to access promoter regions on the DNA through several processes such as DNA and histone methylation, histone acetylation, phosphorylation, and ubiquitination (Berger 2007) play a crucial role in this comorbidity. Tran et al. (2013) showed that rats experiencing stress-induced visceral hypersensitivity had an increase in DNA methylation at the glucocorticoid receptor (GR) promoter and a decrease at the corticotropin-releasing factor (CRF) genes in the amygdala, which resulted in a decrease of the GR and an increase in CRF, respectively. This suggests that methylation related to the HPA-axis might play an important role in the pain-depression comorbidity. In fact, based on a recent study, a potential candidate which might modulate this pattern of methylation might be DNA methyltransferase 3a (Dnmt3a). Wang et al. (2017) suggested that mice vulnerable to mood disorder development after peripheral nerve ligation (PNL) had a reduced protein level of Dnmt3a in the central nucleus of the amygdala. Besides methylation, histone acetylation also seems to be involved in orchestrating the interaction and development of chronic pain and depression. Among the most obvious evidence for this is the notion that the use of histone deacetylase (HDAC) inhibitors has already been considered as a therapeutic strategy for treating both chronic pain and depression (Descalzi et al. 2015; Schroeder et al. 2010). Indeed, Descalzi et al. (2017) showed that HDAC5 was elevated in the nucleus accumbens (NAc) and the periaqueductal gray (PAG) of mice experiencing anxiodepressive-like behaviors due to a spared nerve injury (SNI). In addition, they suggest that knocking out HDAC5 was sufficient to significantly reduce SNI-induced depressive-like behaviors. In accordance with this, Tran et al. (2014) demonstrated that pharmacological deacetylation of H3K9 in the central amygdala of rats after elevated corticosteroid exposure was sufficient to attenuate the anxiety-like behavior, as well as the somatic and visceral hypersensitivity. Indeed, the infusions of histone deacetylase inhibitors into the central amygdala caused a decrease in GR expression and led to a disinhibition of CRF. However, increased deacetylation might be region-specific, since it was found that histone acetylation is increased in the anterior cingulate cortex (ACC), a brain structure known to process both pain- and depression-related stimuli, in mice which express neuropathy-induced depressive-like behaviors (Barthas et al. 2017). Specifically, there was an increased histone H3 lysine 9/lysine 14 (H3K9/K14) acetylation at the promoter regions of *c-Fos* and *Mkp-1*, a gene coding for a critical phosphatase in the mitogen-activated protein kinase pathway. These results (see Table 2) point out the need to further investigate histone modifications in the comorbid relationship of pain and depression since they could constitute a promising target for future treatment strategies.

Although it is still debatable whether microRNAs (miRNAs) should be considered as members of the epigenetic machinery, it is undeniable that they play a significant role in regulating gene expression. They serve as negative posttranscriptional regulators of their target genes and have also been

Table 2 Single-nucleotide polymorphisms and epigenetic factors involved in neuropathic pain and concomitant anxiodepressive-like behaviors

	Expression	Species	Sample	Models	Pain type	Mood disorder	Reference
Single-nucleotide polymorphisms							
[3H] Imipramine sites	Decreased	Human	Platelets	Mianserin treatment	Various	MDD	Magni et al. (1987)
GALR2 SNP	Modulatory	Human	Lymphoblastoid cells	Discectomy	Neuropathic	MDD	Max et al. (2006)
5HTR1A/5HTR2A SNPs	Modulatory	Human	Blood	Lumbar disk surgery	Neuropathic	MDD	Lebe et al. (2013)
BDNF Val66Met SNP	Modulatory	Human	Blood	Genotyping, interview	Various	MDD	Generaal et al. (2016)
Glra3, Gpr88	Increased	Mouse	IC	Endometrios	Visceral	D-L	Li et al. (2018)
Serpina3n	Decreased	Mouse	IC	Endometrios	Visceral	D-L	Li et al. (2018)
Chrnb4, Npas4	Increased	Mouse	HPC	Endometrios	Visceral	D-L	Li et al. (2018)
Lcn2	Increased	Mouse	AMY	Endometrios	Visceral	D-L	Li et al. (2018)
Nptx2	Decreased	Mouse	AMY	Endometrios	Visceral	D-L	Li et al. (2018)
Epigenetics and transcription factors							
GR methylation	Increased	Rat	AMY	Water avoidance stress	Visceral	A-L	Tran et al. (2013)
CRF methylation	Decreased	Rat	AMY	Water avoidance stress	Visceral	A-L	Tran et al. (2013)
H3K9 deacetylation	Increased	Rat	CeA	CORT infusion in CeA	Hyperalgesia	A-L	Tran et al. (2014)
Dnmt3a	Decreased	Mouse	CeA	PNL	Neuropathic	A-L	Wang et al. (2017)
HDAC5	Increased	Mouse	NAc and PAG	SNI	Neuropathic	AD-L	Descalzi et al. (2017)
Lmx1b	Decreased	Mouse	Nervous system	Formalin/carrageenan	Inflammatory	AD-L	Zhao et al. (2007)
p-CREB	Decreased	Mouse	Cortex and HPC	SNI	Neuropathic	AD-L	Li et al. (2017); Zhao et al. (2017)
c-Fos	Increased	Mouse	PFC, ACC, IC, AMY	Zymosan-induced IBS	Spontaneous	A-L	Zhang et al. (2014)
	Increased	Rat	LHb	CMS, formalin injections	Inflammatory	AD-L	Li et al. (2016)
	Increased	Mouse	ACC	SNC	Neuropathic	AD-L	Barthas et al. (2017)

5HTR1A, serotonin 1A receptor; *5HTR2A*, serotonin 2A receptor; *ACC*, anterior cingulate cortex; *AD-L*, anxiodepressive-like; *A-L*, anxiety like; *AMY*, amygdala; *BDNF*, brain-derived neurotrophic factor; *CeA*, central amygdala; *Chrnb4*, cholinergic receptor nicotinic beta 4 subunit; *CMS*, chronic mild stress; *CORT*, corticosteroids; *CRF*, corticotropin-releasing factor; *D-L*, depressive-like; *Dnmt3a*, DNA methyltransferase; *GALR2*, galanin-2 receptor; *Glra3*, glycine receptor alpha 3; *Gpr88*, G protein–coupled receptor 88; *GR*, glucocorticoid receptor; *HDAC5*, histone deacetylase 5; *HPC*, hippocampus; *IBS*, irritable bowel syndrome; *IC*, insular cortex; *IL-6*, interleukin 6; *Lcn2*, lipocalin-2; *LHb*, lateral habenula; *Lmx1b*, LIM homeobox transcription factor 1 beta; *MD*, maternal deprivation; *MDD*, major depressive disorder; *NAc*, nucleus accumbens; *Npas4*, neuronal PAS domain protein 4; *Nptx2*, neuronal pentraxin-2; *PAG*, periaqueductal gray; *p-CREB*, phospho-c-AMP-response element binding; *PFC*, prefrontal cortex; *PNL*, partial sciatic nerve ligation; *Serpina3n*, serpin peptidase inhibitor; *SNC*, sciatic nerve cuffing; *SNI*, spared nerve injury; *SNP*, single-nucleotide polymorphism

shown to target members of the HDAC family in both neuronal and non-neuronal cells (Liu and Liu 2016; Li et al. 2009a). It is thus valuable to consider the role of miRNAs in the comorbidity of chronic pain and depression, alongside the classical epigenetic factors (Descalzi et al. 2015). Masotti et al. (2017) observed a significant negative correlation of circulating serum microRNA miR-320b and depressive symptoms in fibromyalgia patients, which might point to a functional involvement of this miRNA in pain-depression comorbidity. This specific miRNA has been previously associated with neural development, regeneration, and neurite outgrowth (White and Giffard 2012), and it was shown that its expression is disrupted in the blood of patients suffering from complex regional pain syndrome, a condition characterized by neuropathic pain (Orlova et al. 2011).

Transcription factors

However, once the histones unwrap, DNA becomes accessible to transcription factors which regulate transcription and, furthermore, gene expression. Therefore, an increasing number of studies focus on transcription factors involved in the comorbid relationship of chronic pain and mood disorders. A commonly studied transcription factor, the cyclic AMP response element binding (CREB) protein (Hoeffler and Habener 1990), has, among others, a modulating role in the comorbidity of pain and depression. Neuropathic pain–induced depressive-like behaviors in mice caused by SNI are associated with a diminished phospo-CREB expression in both the cortex and hippocampus (Li et al. 2017; Zhao et al. 2017). Furthermore, antidepressants reverse the disrupted phospo-CREB expression associated with pain-induced depressive behaviors (Yasuda et al. 2014), and interestingly, even forced exercise in female mice increases CREB gene expression in pups, which in turn acts anxiolytic and antidepressant and increases the tolerability to pain (Motaghinejad et al. 2017). Consequently, activated CREB can further induce the expression of c-Fos, a marker of neuronal activation (Dragunow and Faull 1989; Hoffman et al. 1993), which is also upregulated by comorbid pain and depression in brain regions associated with modulating pain and emotion such as the prefrontal cortex (PFC), ACC, insular cortex, and amygdala (Zhang et al. 2014). For instance, chronic mild stress paired with formalin-induced pain resulted in greater expression of c-Fos-positive cells in the lateral habenula of rats compared to stress and pain alone (Li et al. 2016). In addition, this upregulation was completely reversed by the antidepressant clomipramine. Similarly, c-Fos was upregulated in the ACC of mice displaying neuropathic pain–induced depressive-like behaviors (Barthas et al. 2017) (see Table 2).

Since serotonin is among the most studied targets in the research of both pain and mood disorders, the transcription factors controlling its expression are also of interest for studying the chronic pain–depression comorbidity. One such candidate is the transcription factor Lmx1b, which is crucial in the differentiation of serotonergic neurons in the nervous system. Zhao et al. (2007) showed that Lmx1b knock-out mice display lowered sensitivity to mechanical stimuli and an enhanced inflammatory pain response. In addition, the effect of antidepressant drugs inhibiting serotonin reuptake was abolished in these mice. These results indicate that the transcription factor Lmx1b has a role in modulating both nociception and depressive-like behaviors (see Table 2).

Another group of transcriptional regulators which were recently demonstrated to play an important role in the comorbidity of pain and depression is the nuclear factor-kappaB (NF-kB) family of transcription factors. They regulate the expression of the metabotropic glutamate receptor 2/3 (mGlu2) in the dorsal horn (DH) and dorsal root ganglia (DRG) (Chiechio et al. 2006). It was shown that treatment with L-acetylcarnitine, a drug commonly prescribed for neuropathies associated with diabetes and HIV, activates NF-kB, which in turn upregulates mGlu2 in the DH and DRG of neuropathic rats and successfully alleviates both their nociceptive- and depressive-like symptoms after only 3 days of treatment (Chiechio et al. 2006; Nasca et al. 2013).

The role of neurotransmitters

Monoamines

Monoamine neurotransmitters including serotonin (5-HT), dopamine (DA), and norepinephrine (NE) are among the most studied candidates in both the field of chronic pain and depression (Haase and Brown 2015). Hence, it is imperative to investigate their role in the molecular mechanisms involved in the comorbidity of these two conditions. The following section will examine some of the present literature concerning the role of these monoamines in the comorbidity of pain and mood disorders (see Table 3).

Serotonin

The serotonergic system has been the focus of a substantial number of pre-clinical and clinical studies on the relation between pain and depression. One widely used method to rapidly induce this comorbidity in rodents relies on the intraplantar administration of complete Freund's adjuvant (CFA) which results in sustained inflammatory pain and leads to depression-like behaviors. This procedure has been shown to deplete serotonin levels, as well as those of its precursors involved in its metabolism in the hippocampus of rats (Zhang et al. 2016a). Similarly, infusing a cocktail of inflammatory agents into the dura mater of rats, inducing meningeal nociception (resembling chronic migraine in humans) and anxiodepressive-like behaviors, resulted in decreased levels of 5-HT in the prefrontal cortex in rats (Zhang et al. 2017). Treatment with the tricyclic antidepressant amitriptyline, commonly used to treat mood disorders, neuropathic pain, and migraine in humans, was able to increase the 5-HT levels and restore the pain- and depression-related behavioral responses (Zhang et al. 2017). However, chronic treatment with the selective-serotonin reuptake inhibitor fluoxetine did not affect the mechanical allodynia, but did block the anxiodepressive-like consequences induced by sciatic nerve injury (Barthas et al. 2017). A single dose of ketamine which is sufficient to alleviate both the mechanical allodynia and the associated depression-like behaviors was also shown to increase the serotonin level in the hippocampus of CFA-administered rats (Zhang et al. 2016a).

As rats primarily rely on their sense of smell to interpret the stimuli in their surroundings, the olfactory bulbectomy (OB) is another model that has been commonly used to induce depressive-like behaviors (van Riezen and Leonard 1990). Interestingly, it also causes an increased nociceptive sensitivity displayed by increased response rates in the hot plate (thermal hyperalgesia) and tail-flick tests (Rodríguez-Gaztelumendi et al. 2014), which makes it suitable for studying the relationship between pain and depression. Moreover, this model was shown to exhibit a downregulation of the

Table 3 Monoamines involved in neuropathic pain and concomitant anxiodepressive-like behaviors

	Expression	Species	Region	Models	Pain type	Mood disorder	Reference
Serotonin							
5-HT	Decreased	Rat	PFC	Dura mater IS infusion	Meningeal	AD-L	Zhang et al. (2017)
IDO1	Increased	Rat	HPC	CFA, chronic social stress	Inflammatory	D-L	Kim et al. (2012)
	Increased	Human	Plasma	Disk herniation, radiculitis	Lumbar/cervical	MDD	Kim et al. (2012)
	Increased	Mouse	HPC, spinal cord	CCI	Neuropathic	D-L	Jiang et al. (2018)
SERT density	Decreased	Rat	Spinal cord	OB	Hyperalgesia	AD-L	Rodríguez-Gaztelumendi et al. (2014)
5HTR1A functionality	Decreased	Rat	Spinal cord	OB	Hyperalgesia	AD-L	Rodríguez-Gaztelumendi et al. (2014)
5-HT/TRP ratio	Decreased	Rat	HPC	CFA injection	Inflammatory	AD-L	Zhang et al. (2016a)
Norepinephrine							
TH-positive cells	Increase	Rat	LC	CCI + CMS	Neuropathic	D-L	Bravo et al. (2014)
α2-Adrenoreceptor	Increase	Rat	LC	CCI	Neuropathic	AD-L	Alba-Delgado et al. (2013)
NAT	Increase	Rat	LC	CCI	Neuropathic	AD-L	Alba-Delgado et al. (2013)
NAT and TH+ cells	Decreased	Rat	LC	STZ-induced diabetes	Hyperalgesia	A-L	Alba-Delgado et al. (2016)
Dopamine							
Extracellular DA	Increase	Rat	NAc	SNI	Neuropathic	D-L	Sagheddu et al. (2015)
D2 receptor	Decrease	Rat	NAc	SNI	Neuropathic	D-L	Sagheddu et al. (2015)
DA level	Decrease	Rat	PFC	Dura mater IS infusion	Meningeal	AD-L	Zhang et al. (2017)
DA release	Increase	Rat	NAc	SNL	Neuropathic	AD-L	Kato et al. (2016)

5-HT, serotonin; *5HTR1A*, serotonin 1A receptor; *A-L*, anxiety-like; *AD-L*, anxiodepressive-like; *CCI*, chronic constriction injury; *CFA*, complete Freund's adjuvant; *CMS*, chronic mild stress; *DA*, dopamine; *D-L*, depressive-like; *HPC*, hippocampus; *IDO1*, indoleamine 2,3-dioxygenase 1; *IS*, inflammatory soup; *LC*, locus coeruleus; *MDD*, major depressive disorder; *NAc*, nucleus accumbens; *NAT*, noradrenaline transporter; *OB*, olfactory bulbectomy; *PFC*, prefrontal cortex; *SERT*, serotonin transporter; *SNI*, spared nerve injury; *SNL*, spinal nerve ligation; *STZ*, streptozotocin; *TH*, tyrosine hydroxylase; *TRP*, tryptophan

serotonin transporter and receptor 1A (5-HT1A) functionality in DH of the lumbar spinal cord. The group showed that chronic, but not acute, treatment of OB rats with fluoxetine progressively normalized both the nociceptive responses and depressive-like behaviors, and also restored the transporter density and receptor functionality to normal levels. These findings highlight the role of serotonin signaling at the periphery in the comorbidity of pain and depression.

Besides looking strictly at the serotonin neurotransmitter and its receptor, research has recently focused on studying promising molecular candidates which are involved in its metabolism. It was found that indoleamine 2,3-dioxygenase 1 (IDO1), a rate-limiting enzyme in tryptophan metabolism, is responsible for a decrease of serotonin content in chronic pain–induced mood disorders (Kim et al. 2012). Inhibiting the elevated presence of this precursor of serotonin in the hippocampus of rats and mice attenuated their depressive-like behaviors caused by inflammatory pain and social stress (Kim et al. 2012; Zhang et al. 2016a). A similar increase in the presence of IDO1 was also found in the plasma of human patients who suffered from disk herniation or radiculitis for more than 3 months, which subsequently led to the development of depression (Kim et al. 2012). These results suggest that neurometabolic changes related to serotonin signaling can play a modulatory role in the comorbidity of chronic pain and depression.

Norepinephrine

Alongside serotonin, NE signaling is another prominent target for both studying and treating the comorbid occurrence of pain and mood disorders. Its primary source, the locus coeruleus (LC) nucleus, has been closely associated with nociception and emotion and might play a key role in this comorbidity.

By combining the models of chronic constriction injury (CCI) and chronic mild stress (CMS), it has been found that chronic pain and chronic stress mutually potentiate each other, resulting in more pronounced changes in the noradrenergic transmission compared to the effect of each condition alone (Bravo et al. 2013, 2014). For instance, comorbid neuropathic pain and stress-induced depressive-like behaviors resulted in an increased expression of tyrosine hydroxylase, the rate-limiting enzyme of NE synthesis, in LC neurons, which also showed a decrease in spontaneous electrophysiological activity. Moreover, prolonged neuropathy induced by CCI also enhanced the expression and sensitivity of alpha 2 adrenoreceptor and increased the expression of the norepinephrine transporter (NET) in the LC of rats (Alba-Delgado et al. 2013). Interestingly, this increase in expression was time-dependent and coincided with the onset of anxiodepressive-like behaviors (28 days post-CCI). These findings point to several modifications related to noradrenergic transmission in the LC in pain and depression comorbidity.

Subsequent research showed that different types of neuropathic pain can employ opposite molecular and neuroplastic mechanisms to result in the development of comparable anxiodepressive-like behaviors. Namely, rats administered with a single systemic injection of streptozotocin (STZ) displayed aspects of type 1 diabetes and showed a gradual increase in nociceptive hypersensitivity. Curiously, although the temporal development of hypersensitivity in these animals was different than in CCI rats, the onset of anxiety-like and depressive-like behaviors was observed at the same time delay (28 days after neuropathy induction). However, in contrast to what is observed in CCI rats, STZ rats showed a decrease in tyrosine hydroxylase and NET levels in the LC, as well as in the overall LC firing activity (Alba-Delgado et al. 2016). This indicates that specific neuroplastic mechanisms take place in different models of pain-depression comorbidity and highlight the importance of studying different models of chronic pain and mood disorders, since it seems that each type induces specific molecular and cellular alterations.

The role of NE in the comorbid relationship between chronic pain and mood disorders has also been demonstrated through clinical treatment of patients with pharmacological agents targeting its synaptic presence. Alongside the commonly used duloxetine, an efficient agent in treating negative symptoms of fibromyalgia, milnacipran, a serotonin norepinephrine reuptake inhibitor (SNRI) with greater affinity for the NE reuptake site (Goldenberg et al. 2010), has been shown to alleviate discomfort, fatigue, and physical dysfunction, while continued treatment gradually improves symptoms of pain and depression. Moreover, besides their antidepressant effect, acute or chronic treatment with norepinephrine reuptake inhibitors (NRIs) such as desipramine and reboxetine has shown robust anti-allodynic and/or anti-hyperalgesic effect in rodents (Leventhal et al. 2007; Yalcin et al. 2009). Also, other compounds which have been shown to have a high selectivity for the NE transporter have provided promising results, such as the conopeptide Xen2174 which produced a long-lasting anti-allodynic response in CCI and SNL rats (Nielsen et al. 2005), or WAY-318068 which, alongside depression, showed efficacy in models of neuropathic, acute, inflammatory, visceral, diabetic, and cancer pain (Whiteside et al. 2010). Hence, although SNRIs may produce more pronounced effects on the pain-depression comorbidity compared to NRIs or SSRIs alone, it is still important to fully elucidate the individual role of each monoamine, in order to better optimize current and new treatment strategies.

Dopamine

Alongside 5-HT and NE, there is compelling evidence that DA is also implicated in the comorbid relationship of pain and depression through its spinal and supraspinal activity involving several brain regions such as the periaqueductal gray (PAG), the thalamus, the basal ganglia, and the limbic system (Hache et al. 2011).

As seen with 5-HT, an infusion of an inflammatory soup in the dura mater of rats, causing a migraine-type of pain-related anxiodepressive-like behaviors, also results in a decrease of DA levels in the PFC. Again, these molecular and phenotypic effects were improved by treatment with the tricyclic antidepressant amitriptyline (Häuser et al. 2008).

Several studies have shown that the neuropathy-induced anxiety and depressive-like behaviors are closely linked to the DA receptor expression, as well as DA release in the rat NAc (Sagheddu et al. 2015; Kato et al. 2016). Specifically, during the early phase of neuropathic pain (2 weeks post-SNI), there is a decrease in DA-2 receptor expression in the NAc of rats (Sagheddu et al. 2015), which is also seen after chronic mild stress (Papp et al. 1994). Accordingly, it has been demonstrated that treatment with commonly used post-surgical pain relief medications such as clonidine or gabapentin during 14 days after SNL increased intra-NAc DA release in rats with neuropathic pain (Xie et al. 2014). Curiously, the same pattern of early phase DA increase in the NAc was also observed after pain relief due to pregabaline treatment or 30% sucrose intake after SNL, suggesting that pain relief might be triggering a reward-like mechanism through DA signaling, which has an effect on the overall mood-related state of the animal (Kato et al. 2016). However, this pattern of DA release after pain relief or sucrose intake was not persistent, and it faded in a later phase of neuropathy (4 weeks after SNL) (Stoy et al. 2012). Interestingly, a hypodopaminergic state is also commonly reported in patients suffering from Parkinson's disease, which is associated with a high incidence of both depression and chronic pain (Conte et al. 2013). These results accentuate the role of altered dopaminergic function in the comorbid development of mood disorders such as depression, and chronic pain, and emphasize the need for further studies regarding the role of DA in these conditions.

Instead of focusing on the individual role of 5-HT, NE, and DA in mediating pain and depression, some studies have looked at the combined action of all three of them in modulating this comorbid relationship. Direct evidence for this comes from a new class of antidepressants, known as the triple reuptake inhibitors. As their name suggest, these compounds simultaneously inhibit the reuptake of 5-HT, NE, and DA, thereby prolonging their presence and activity at postsynaptic levels (Guiard et al. 2009). It was recently shown that commercially available triple reuptake inhibitor drugs such as indatraline, as well as newly synthesized and structurally different ones, such as NS18283, significantly reduce nociceptive hypersensitivity and depressive-like behaviors in a mouse model of chemotherapy-induced neuropathic pain (Hache et al. 2015). Hence, all of these studies, whether tackling the role of monoamines separately or as a group, shed light on the complex nature of the comorbid development of pain and depression.

Glutamate and GABA

Glutamate and gamma-aminobutyric acid (GABA) are the major excitatory and inhibitory neurotransmitters in the nervous system, respectively. The balance between excitation and inhibition guarantees the well-functioning of the brain. Excessive plasma glutamate/glutamine and a significantly lower GABA level were detected in patients with major depression (Northoff and Sibille 2014). Further studies found that drugs targeting glutamate transmission, like the NMDA antagonist ketamine, could alleviate both pain and depressive symptoms in both animals and humans (Ettensohn et al. 2018; Wang et al. 2011), and the AMPA receptor facilitator AMPAkines has similar analgesic and antidepressant effects by acting on the descending inhibitory circuits such as the PAG-rostral ventromedial medulla (RVM) and the NAc-RVM axes (Le et al. 2014) (see Table 4).

Glutamate

A disrupted level of glutamatergic transmission and glutamatergic receptors has been demonstrated in animal models of chronic pain and mood disorder comorbidity (see review of Benson et al. 2015). For instance, enhanced presynaptic glutamate neurotransmission in the ACC, the higher structure for integrating the affective component of painful sensation and mood disorders, was observed in both chronic inflammatory pain (Zhao et al. 2006a, b) and neuropathic pain (Koga et al. 2015). More specifically, Koga and colleagues showed enhanced presynaptic glutamate release probability (Koga et al. 2015; Zhuo 2016), since lower paired-pulse ratio (PPR) was observed in the ACC of mice displaying chronic pain–induced anxiety. Furthermore, they reported that blocking the hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, which are involved in pre-long-term potentiation (LTP), produced analgesic and anxiolytic effects (Koga et al. 2015). In vivo electrophysiological recordings also support the idea that the ACC is hyperactive when animals display chronic pain and depression comorbidity. Interestingly, the temporal inhibition of the glutamatergic neuron of the ACC by optogenetic stimulation blocked the anxiodepressive-like consequences of neuropathic pain (Sellmeijer et al. 2018). In contrast, it has been shown that the decreased activity of pyramidal neurons in the prelimbic cortex plays an essential role in pain-induced affective symptoms (Wang et al. 2015; Kelly et al. 2016) and that an increased GABAergic inhibition is responsible for the reduction of pyramidal activity (Zhang et al. 2015).

Metabotropic glutamate receptors

Metabotropic glutamate receptors (mGluRs) are members of the class C family of G protein–coupled receptors, regulating glutamatergic transmission in the CNS. Currently, there are three groups and eight subtypes of mGluRs which have been identified. Group I (mGluR1 and mGluR5) are excitatory G protein–coupled and predominantly expressed post-synaptically, whereas group II (mGluR2/3) and group III (e.g., mGluR4) are inhibitory G protein–coupled and mostly pre-synaptically expressed (see Chiechio 2016 for review). These receptors are involved in many physiological process and diseases like chronic pain (Chiechio 2016) and mood disorders (Zarate et al. 2010). Postmortem studies in major depressive disorder (MDD) and bipolar disorder patients revealed no mGluR (mGluR2/3 and mGluR5) alterations in the ACC (Matosin et al. 2014); however, mGluR2/3 was elevated in the PFC in MDD (Feyissa et al. 2010). mGluR4, expressed in both GABAergic and glutamatergic synapses in the amygdala, modulates sensory and affective components of pain. Indeed, Zussy et al. (2016) showed that the activation of mGluR4, by a photopharmacological approach, reversibly inhibited anxiodepressive consequences of inflammatory pain. Chung et al. (2017) injected [11C] ABP688, an mGluR5-selective radiotracer, via the rat tail vein and used positron-emission tomography to examine the expression level of mGluR5 in different brain regions 16–25 days after spared nerve ligation (SNL). Interestingly, they found bidirectional changes of mGluR5 expression indicating an upregulation in the caudal part of the prelimbic (PrL) cortex and downregulation in the insular cortex and NAc. However, pharmacological blockage of mGluR5 in the PrL was sufficient to ameliorate both tactile hypersensitivity and depressive-like behaviors.

Table 4 Role of the glutamatergic/GABAergic transmission in neuropathic pain and concomitant anxiodepressive-like behaviors

	Expression	Species	Region	Models	Pain type	Mood disorder	Reference
Glutamate and GABA							
Glutamate release	Increased	Mouse	ACC	CFA-injection	Inflammatory	A-L	Zhao et al. 2006a, b; Koga et al. (2015)
mGluR5	Increased	Rat	PrL	SNL	Neuropathic	D-L	Chung et al. (2017)
	Decreased	Rat	IC, NAc	SNL	Neuropathic	D-L	Chung et al. (2017)
GluA1	Increased	Rat	NAc	SNI	Neuropathic	D-L	Goffer et al. (2013); Su et al. (2015)
	Increased	Rat	NAc	CFA injection	Inflammatory	D-L	Su et al. (2015)
	No difference	Rat	NAc	Paw incision	Post-incisional	D-L	Su et al. (2015)
	No difference	Mouse	AMY	Reserpine treatment	Hyperalgesia	D-L	Liu et al. (2014)
GluN2A	No difference	Mouse	AMY	Reserpine treatment	Hyperalgesia	D-L	Liu et al. (2014)
	Increased	Rat	rACC	Formalin injection	Inflammatory	CPA	Li et al. (2009b)
GluN2B	Increased	Rat	rACC	Formalin injection	Inflammatory	CPA	Li et al. (2009b)
	Increased	Mouse	AMY	Reserpine treatment	Hyperalgesia	D-L	Liu et al. (2014)
pGluN1	Decreased	Rat	HPC	CCI	Neuropathic	AD-L	Li et al. (2014)
GluN1	No difference	Rat	rACC	Formalin injection	Inflammatory	CPA	Li et al. (2009b)
GABA	Decreased	Human	Mid-ACC	Osteoarthritis	Joint pain	MDD	Reckziegel et al. (2016)

ACC, anterior cingulate cortex; *AD-L*, anxiodepressive-like; *A-L*, anxiety-like; *AMY*, amygdala; *CCI*, chronic constriction injury; *CFA*, complete Freund's adjuvant; *CPA*, conditioned place avoidance; *D-L*, depressive-like; *GABA*, gamma-aminobutyric acid; *GluA1*, AMPA receptor subunit; *GluN1*, NMDA receptor subunit zeta-1; *GluN2A*, NMDA receptor 2A; *GluN2B*, NMDA receptor 2B; *HPC*, hippocampus; *IC*, insular cortex; *MDD*, major depressive disorder; *mGluR5*, metabotropic glutamate receptor 5; *NAc*, nucleus accumbens; *pGluN1*, phosphorylated GluN1; *PrL*, prelimbic region; *rACC*, rostral anterior cingulate cortex; *SNI*, spared nerve injury; *SNL*, spinal nerve ligation

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors

AMPA, NMDA, and kainate receptors are ionotropic glutamate receptors, exerting faster effects than metabotropic receptors. α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are tetramers composed of four types of subunits: GluA1, GluA2, GluA3, and GluA4. It has been shown that the expression of AMPA is altered in the comorbidity of chronic pain and mood disorders. GluA1 AMPA receptor subunit, for example, was reported increased in the NAc in the SNI rat model (Goffer et al. 2013). Su et al. (2015) confirmed the elevated GluA1 level in NAc of SNI rat model, and more specifically, they compared the GluA1 and GluA2 expression levels in three different models displaying pain-depression comorbidity conditions: post-incisional pain with paw incision (PI), persistent but reversible inflammatory pain (CFA), and chronic neuropathic pain (SNL) models. Their results showed that the GluA1 level in NAc synapses was not altered in the PI model, increased 7 days after CFA injection (but recovered 14 days after), and increased and remained unchanged in SNL model. Both studies (Su et al. 2015; Goffer et al. 2013) point to a unique adaptive mechanism of GluA1 in different types of chronic pain and depression comorbidity. The overexpression of GluA1 subunit exclusively increases the synthesis of the Ca^{2+}-permeable AMPA receptors which are formed by GluA1 homomers, whereas blocking these homomers worsens depressive symptoms (Su et al. 2015).

N-methyl-D-aspartate receptors

N-methyl-D-aspartate (NMDA) receptors are the most studied glutamatergic receptors in the context of depression and chronic pain due to their role in regulating the glutamatergic system and plasticity changes like postsynaptic LTP. Ketamine, a noncompetitive NMDA antagonist, exerts fast antidepressant and analgesic effects (see Zorumski et al. 2016 for review) at a subanesthetic dose. It also blocks the anxiodepressive-like consequences of neuropathic pain in rodents after an administration of a single subanesthetic dose (Wang et al. 2011). In a reserpine-induced pain/depression model, an upregulation of GluN2B, but not GluN2A or AMPA receptor GluA1 expression, was observed in the amygdala of mice (Liu et al. 2014). However, a decreased phosphorylation of the NMDA receptor type 1 (GluN1) in the hippocampus was reported in rats showing anxiety and depressive-like behaviors following CCI (Li et al. 2014). In addition, GluN2A and GluN2B, but not GluN1, were upregulated in the rostral ACC in formalin-injected rats, and selectively blocking these subunits abolished the acquisition of the induced conditioned place avoidance indicating the critical role of the NMDA in pain-related aversion (Li et al. 2009b). Also, it has been recently shown that the neuropathy-induced

Table 5 Role of the endocannabinoids in neuropathic pain and concomitant anxiodepressive-like behaviors

Endocannabinoids							
2-AG	Increased	Human	Plasma	Osteoarthritic pain	Joint pain	MDD	La Porta et al. (2015)
CB1 and CB2 mRNA	Increased	Human	Lymphocytes	Osteoarthritic pain	Joint pain	MDD	La Porta et al. (2015)
AEA	Decrease	Rat	HPC and PFC	WKY (stress-prone strain)	Allodynia	AD-L	Vinod et al. (2012)
CB1 coupling	Decrease	Rat	HPC and PFC	WKY (stress-prone strain)	Allodynia	AD-L	Vinod et al. (2012)
AEA/2-AG	Decrease	Mouse	Brain + GS muscle	CUS + intramuscular NGF	Hyperalgesia	AD-L	Lomazzo et al. (2015)

2-AG, 2-arachidonoylglycerol; *AD-L*, anxiodepressive-like; *AEA*, anandamide; *CB1*, cannabinoid receptor type 1; *CB2*, cannabinoid receptor type 2; *CUS*, chronic unpredictable stress; *GS*, glutamine synthetase; *HPC*, hippocampus; *MDD*, major depressive disorder; *NGF*, nerve growth factor; *PFC*, prefrontal cortex; *WKY*, Wistar Kyoto rat

anxiodepressive-like behaviors could be attributed to an NMDA-contributed hyperactivity of the ACC (Sellmeijer et al. 2018).

Kainate receptors

In addition to AMPA and NMDA receptors, kainate receptors form another group of ionotropic glutamatergic receptors. It has been clearly shown that kainate receptors mediated pre-LTP, increased glutamate release probability measured by paired-pulse facilitation, are implicated in the CFA-induced anxiety-like behaviors (Koga et al. 2015).

GABA

The GABAergic system is studied in both human and pre-clinical animal models, contributing to the overall understanding of GABA level in different brain regions and different pain and mood disorder comorbidity cases. For instance, using proton magnetic resonance spectra optimized for detecting GABA level in patients with osteoarthritis, it has been shown that altered GABA level in mid-ACC is only responsible for pain severity but not affective compound (Reckziegel et al. 2016). In a rat model of chronic inflammatory pain, GABA expression is elevated in mPFC, and administering a GABA_A antagonist could improve mechanical allodynia (Luongo et al. 2013). Another study which focused on the pain-depression comorbidity showed that intra-basolateral amygdala (BLA) administration of muscimol, a GABA_A agonist, decreased formalin-induced pain behavior in CMS rats and increased their sucrose preference, while intra-mPFC administration of muscimol produced no effect, suggesting different roles of the BLA and mPFC mediating pain perception in depressive states and highlighting the brain region–dependent role of GABAergic system (Qi et al. 2013). Similarly, intraperitoneal injections of pregabalin, an alkylated analog of GABA, improved nociceptive, anxiety-like, and anhedonic responses in neuropathic pain induced by PSNL mice model (La Porta et al. 2016), further strengthening the evidence for the role of the GABAergic system in the pain-depression comorbidity.

The endocannabinoid system

There are various accounts from around the world that the plant *Cannabis sativa* has been utilized as medicine for thousands of years (Fitzgibbon et al. 2015). Its main psychoactive compound, delta-9-tetrahydrocannabinol (Δ9-THC), was identified in 1964 (Gaoni and Mechoulam 1964). Successive studies on its activity resulted in the identification of the endocannabinoid system. This system is comprised of the cannabinoid receptors (CB1 and CB2) and their endogenous ligands, with anandamide (AEA) (Devane et al. 1992) and 2-arachidonylglycerol (2-AG) (Mechoulam et al. 1995) being the most investigated ones.

While clinical evidence is still scarce when it comes to the role of the endocannabinoid system in the pain-depression comorbidity, there are several studies suggesting that it is a valid target for future research. For instance, La Porta et al. (2015) found a significant positive correlation between 2-AG plasma levels in osteoarthritic patients with their levels of pain and depression. Moreover, they also report a positive correlation of depression with CB1 mRNA expression in blood lymphocytes and CB2 with pain scores. However, probably the highest number of clinical evidence linking the endocannabinoid system to pain and depression comorbidity comes from the use of cannabis and its natural and synthetic counterparts in patient treatment. Woolridge et al. (2005) report that cannabis intake was associated with decreased muscular and neuropathic pain, alongside anxiety and depression in HIV patients. Similarly, there was a significant pain and depression reduction in fibromyalgia patients after 4 weeks of treatment with nabilone (a Δ9-THC analog), compared to the placebo group (Skrabek et al. 2008).

In spite of a number of studies linking endocannabinoid modulation with pain and depression alone, there is limited pre-clinical evidence associating the co-occurrence of chronic pain and depression to the endocannabinoid system (Fitzgibbon et al. 2015). Nevertheless, Vinod et al. (2012) found that Wistar Kyoto rats, a genetically stress-prone strain displaying increased depressive- and anxiety-like behaviors as well as exacerbated mechanical allodynia, showed decreased

Table 6 Role of the BDNF in neuropathic pain and concomitant anxiodepressive-like behaviors

	Expression	Species	Region	Models	Pain type	Mood disorder	Reference
BDNF	Decreased	Mouse	HPC	SCI	Neuropathic	D-L	Li et al. (2017)
	Decreased	Rat	HPC	CFA-injection	Inflammatory	D-L	Duric and McCarson (2006, 2007)
	Decreased	Mouse	Cortex, HPC	PSNL	Neuropathic	D-L	Brüning et al. (2015)
	Decreased	Rat	ACC, mPFC, HPC	SNI	Neuropathic	D-L	Pan et al. (2018)
	Decreased	Mouse	ACC	SNI	Neuropathic	D-L	Zhao et al. (2017)
	Decreased	Rat	ACC	CCI	Neuropathic	D-L	Ishikawa et al. (2014)
	Decreased	Rat	ACC, RVM	CCI	Neuropathic	D-L	Yasuda et al. (2014)
	Decreased	Mouse	ACC, BLA, CA1/3, RVM	SNL	Neuropathic	D-L	Zhu et al. (2017)
	Decreased	Mouse	mPFC	SNI	Neuropathic	D-L	Guida et al. (2015)
	Decreased	Rat	PFC	SNI	Neuropathic	D-L	Xie et al. (2017)
	Decreased	Mouse	mPFC	CMS	Hyperalgesia	D-L	Liu et al. (2018)
	Increased	Rat	rACC	SNI	Neuropathic	CPA	Zhang et al. (2016b)
	Increased	Human	Colonic biopsies	IBS	Visceral pain	MDD	Yu et al. (2011)
	Increased	Rat	Spinal cord	SNL	Neuropathic	D-L	Wei et al. (2017)
	No difference	Mouse	PFC	PSNL	Neuropathic	A-L	González-Sepúlveda et al. (2016)
	No difference	Human	Serum level	Musculoskeletal pain	Musculoskeletal	MDD	Generaal et al. (2016)

ACC, anterior cingulate cortex; *A-L*, anxiety-like; *BDNF*, brain-derived neurotrophic factor; *BLA*, basolateral amygdala; *CCI*, chronic constriction injury; *CFA*, complete Freund's adjuvant; *CMS*, chronic mild stress; *CPA*, conditional place avoidance; *D-L*, depressive-like; *HPC*, hippocampus; *IBS*, irritable bowel syndrome; *MDD*, major depressive disorder; *mPFC*, medial prefrontal cortex; *PFC*, prefrontal cortex; *PSNL*, partial sciatic nerve ligation; *rACC*, rostral ACC; *RVM*, rostral ventromedial medulla; *SNI*, spared nerve injury; *SNL*, spinal nerve ligation

levels of AEA and increased levels of CB1 coupling in the hippocampus and frontal cortex. Another direct evidence connecting the pain-depression comorbidity with the endocannabinoid system comes from Lomazzo et al. (2015) who utilized the CMS mouse model in combination with intramuscular administration of nerve growth factor to achieve anxiodepressive-like behaviors and widespread mechanical hyperalgesia. They showed that pretreatment of these mice with URB597, an inhibitor of the fatty acid amide hydrolase (FAAH), which is the primary enzyme responsible for the metabolism of AEA, was sufficient to attenuate anxiety-like behaviors in the light-dark test, as well as thermal and widespread mechanical hyperalgesia. Similarly, Hu et al. (2009) utilized the CCI model to investigate the interaction between the CB2 receptor and the comorbid chronic pain and depressive-like behavior. They showed that a systemic administration of GW405833, a CB2 agonist, significantly lowered the CCI-induced depressive-like behaviors and mechanical hyperalgesia, pointing to its potential as an alternative treatment option.

Together, although limited, current evidence suggests a promising role of the endocannabinoid system (see Table 5) in the interactive relationship of chronic pain and depression, and constitutes a valid target for future studies, which could aim at delineating whether the effects observed in the comorbidity follow the same or separate molecular pathway.

Neurotrophic factors

Changes in neurotrophic factors, particularly BDNF, and subsequent alterations in synaptic plasticity and synapse dynamics contribute to the comorbidity of chronic pain and depression. BDNF is the most widely expressed neurotrophin in the peripheral and central nervous system where it regulates neuronal survival and differentiation and critically participates in activity-dependent synaptic plasticity mechanisms (see review of Bramham and Messaoudi 2005). Clinical studies showed increased plasma BDNF levels in patients with fibromyalgia (Haas et al. 2010) and IBS (Yu et al. 2011) displaying severe depressive symptoms. However, pre-clinical studies suggest a region-dependent manner of BDNF regulation in both chronic pain and in depression. Indeed, BDNF transcription and expression is upregulated immediately (24 h) after CFA injection in the DH of rats and remains high even 14 days post-injection (Duric and McCarson 2006, 2007). Consistent with chronic inflammation, the BDNF level in the spinal cord in neuropathic pain models is significantly higher than in the sham group in both mice (Almeida et al. 2015) and rats (M'Dahoma et al. 2015; Zhang et al. 2016b; Wei et al. 2017; Tateiwa et al. 2018). Despite the uniform upregulation of BDNF in the spinal cord, alterations in the hippocampus are time-dependent.

Table 7 Role of neurogenesis in neuropathic pain and concomitant anxiodepressive-like behaviors

	Expression	Species	Region	Models	Pain type	Mood disorder	Reference
Neurogenesis							
BrdU+ cells	Decrease	Rat	DG	CFA, immobilization	Inflammatory	A-L	Duric and McCarson (2006)
DCX+/BrdU+ cells	Decrease	Mouse	HPC	SNI	Neuropathic	A-L	Mutso et al. (2012)
DCX+/BrdU+ cells	Decrease	Mouse	DG	Chronic CFA	Inflammatory	A-L	Zheng et al. (2017)
DCX+/BrdU+ cells	Decrease	Rat	HPC	CCI, immobilization	Neuropathic	A-L	Romero-Grimaldi et al. (2015)

A-L, anxiety-like; *BrdU*, bromodeoxyuridine; *CCI*, chronic constriction injury; *CFA*, complete Freund's adjuvant; *DCX*, doublecortin; *DG*, dentate gyrus; *HPC*, hippocampus; *SNI*, spared nerve injury

The hippocampal transcription and expression level of BDNF decreased right after CFA-injection in rats and remains low (Duric and McCarson 2007). In contrast to the quick drop in the chronic inflammatory model, the reduction of hippocampal BDNF level is slower in the neuropathy cases. For instance, BDNF expression began to downregulate at least 7 days after SCI (Li et al. 2017), SNL (Zhu et al. 2017), PSNL in mice (Brüning et al. 2015), and SNL in rats (Tateiwa et al. 2018), when the depressive-like symptoms emerged. These suggest on the one hand that neuropathic pain has a different mechanism than inflammatory pain, and on the other hand that the opposite regulatory direction of BDNF level in the spinal dorsal horn and hippocampus is due to their different roles in the pain chronification. Respectively, fast and slow regulations also hint at potential interactions between BDNF derived from different sources such as nociceptor neurons, peripheral sensory neurons, and microglia-derived BDNF.

In the forebrain regions like mPFC and ACC, most of the neuropathy studies reported downregulation of BDNF in the SNI model of both rats (Xie et al. 2017; Pan et al. 2018) and mice (Guida et al. 2015; Zhao et al. 2017; Zhu et al. 2017), and CCI rat model (Ishikawa et al. 2014; Yasuda et al. 2014). Moreover, BDNF levels in BLA and RVM were also reported to be downregulated in the SNL mouse model (Zhu et al. 2017) and CCI rat model (Yasuda et al. 2014). There are also some negative results regarding BDNF level changes in neuropathy cases. For instance, contrary to their results in the hippocampus, Tateiwa et al. (2018) reported an unchanged BDNF expression level in other brain regions like the mPFC and ACC, as well as thalamus, cerebellum, and amygdala, 21 days after nerve injury in the SNL model. González-Sepúlveda et al. (2016) also detected no difference in the PFC BDNF level in a PSNL mice model with comorbid anxiety-like behavior. Curiously, one of the common features of the latter studies is the fact that at the time point at which the animals were tested, they did not show any depressive-like behavior; however, according to the Xie et al. (2017), BDNF level changes occur only when there are comorbid pain and depressive-like symptoms observed (see Table 6).

Neurogenesis

Adult neurogenesis is commonly assessed by administering bromodeoxyuridine (BrdU), an analog of thymidine, to detect cells that are actively replicating their DNA, and therefore proliferating (Lehner et al. 2011). Another method involves labeling the microtubule binding protein doublecortin (DCX) which is transiently expressed in proliferating progenitor cells and newly generated neuroblasts (Brown et al. 2003). These techniques are very useful in pre-clinical studies, including those using rodent models to demonstrate a relationship between chronic pain–depression comorbidity and altered neurogenesis in the adult hippocampus. For instance, Duric and McCarson (2006) showed that BrdU-positive cells in the dentate gyrus of rats were significantly reduced after exposure to prolonged inflammation (21 days of CFA) or stress (repeated immobilization for 10 days). Moreover, it was demonstrated that both SNI and CFA models in mice result in a reduction of $DCX^+/BrdU^+$ neuroblasts (Mutso et al. 2012; Zheng et al. 2017). Interestingly, Romero-Grimaldi et al. (2015) found that stress (i.e., chronic immobilization stress) significantly exacerbated the negative effects of CCI and resulted in even greater reduction of proliferation, survival, and differentiation of rat newborn hippocampal cells (see Table 7). Although the research on the relationship of depression and neurogenesis has been recently subjected to serious discrepancies (Hanson et al. 2011), the amount of information available is still exceedingly high in comparison to the very limited information that is available on the potential implications of neurogenesis in chronic pain (Grilli 2017). Therefore, even though the available data suggest that hippocampal neurogenesis is affected and implicated in both chronic pain and mood disorders, its full role is in each of the conditions, and their comorbidity remains to be determined.

Neuroendocrine alterations

Although still not fully elucidated, the role of the hypothalamic-pituitary-adrenal (HPA) axis, one of the main bodily stress response systems, is likely also playing a role in the relationship of chronic pain and mood disorders. Intriguingly, in both the CCI model and the sciatic nerve cuffing model of neuropathic pain–induced depressive-like behaviors, there was no alteration in the HPA axis (Bomholt et al. 2005; Ulrich-Lai et al. 2006; Kilburn-Watt et al. 2010; Yalcin et al. 2011). On the other hand, it was shown in patients with chronic multi-site musculoskeletal pain who suffer from major depressive disorder that pain induces hypoactive HPA axis function while depression causes a hyperactive function, so it is possible that these two conditions might blunt the individual effect of each other (Generaal et al. 2014). Moreover, Bomholt et al. (2005) observed that in CCI rats, the HPA axis responded normally to novel stressors which are known to activate the HPA axis. Similarly, Ulrich-Lai et al. (2006) reported that the CCI did not affect resting or restraint stress-related HPA activity. However, these studies focused on a specific pain model and, more importantly, only on the presence of corticosteroid and cortisol, the dominant glucocorticoids found in rodents and humans, respectively. Therefore, such approach likely provides incomplete information about the role, if any, of the HPA axis in subjects with pain-depression comorbidity. Hence, it is important to look further into other models and candidate hormones involved in the activation of the HPA axis to determine its participation in the comorbid relationship of pain and depression. For instance, it was shown that female patients who developed depression due to chronic mandibular pain show no difference in cortisol levels compared to healthy controls, but have a decreased dehydroepiandrosterone (DHEA) secretion, which is another highly abundant hormone in the HPA axis, associated with pain intensity, stress, and pain-related depressive states (Jo et al. 2016). Moreover, there is an increase in serum adrenocorticotropic hormone (ACTH) and corticosterone levels in mice submitted to PSNL model, additionally pointing to a role of the HPA axis activation in the pain-depression comorbidity (Brüning et al. 2015). Also, a study by Ji et al. (2007) showed that the function of the corticotrophin releasing hormone receptor CRH1 in the amygdala is implicated in pain-related anxiety-like behavior. Namely, systemic and intra-amygdalar administration of the CRH1 antagonist NBI 27914 was sufficient to reduce the nociceptive and anxiety-like responses in a rat model of arthritic pain. This is in accordance with the results obtained by Ulrich-Lai et al. (2006) which show an increase in the expression of corticotrophin releasing hormone mRNA in the central amygdala of rats after CCI model.

On the other hand, Kilburn-Watt et al. (2010) found a decrease in thyroid hormones in rats which displayed an altered social behavior following a sciatic nerve ligation. Unexpectedly, the decrease was persistent indicating an altered regulation of the hypothalamic-pituitary-thyroid axis. Similarly, other studies also reported that there was an association between thyroid autoimmunity with fibromyalgia and depression (Pop et al. 1998; Ribeiro and Proietti 2004). Interestingly, Pamuk and Cakir (2007) observed that thyroid autoimmunity in fibromyalgia was characteristic of older postmenopausal female patients, suggesting a possible role of estrogen. Indeed, there is cumulative evidence demonstrating the role of the estrogen receptor in various molecular and cellular functions associated with depression and pain processing (Lu and Herndon 2017). This goes in line with a recent finding that endometriosis, an estrogen-dependent inflammatory disorder associated with chronic pelvic pain, anxiety, and depression, triggers differential gene expression in several brain regions (Li et al. 2018). Specifically, mice with endometriosis displayed depressive-like behaviors and nociceptive hypersensitivity, which were accompanied by disrupted expressions of several genes such as Gpr88, Glra3, and Serpina3n in the insula, Chrnb4 and Npas4 in the hippocampus, and Lcn2 and Nptx2 in the amygdala, which are associated with anxiety and chronic pain.

Taken together, the results of these studies (see Table 8) point to a multifaceted role of hormones in the comorbidity of pain and depression and therefore, constitute a justified

Table 8 Role of hormones in neuropathic pain and concomitant anxiodepressive-like behaviors

	Expression	Species	Samples	Models	Pain type	Mood disorder	Reference
Hormones							
CRF1R	Increased	Rat	AMY	Kaolin/carrageenan	Arthritic	AD-L	Ji et al. (2007)
CRF mRNA	Increased	Rat	AMY	CCI	Neuropathic	AD-L	Ulrich-Lai et al. (2006)
Cortisol/DHEA	Increased	Human	Saliva	TMD + BDI-II	Mandibular	MDD	Jo et al. (2016)
ACTH and CORT	Increased	Mouse	Serum	PSNL	Neuropathic	AD-L	Brüning et al. (2015)
Thyroid hormones	Decreased	Rat	Plasma	CCI	Neuropathic	AD-L	Kilburn-Watt et al. (2010)

ACTH, adrenocorticotropic hormone; *AD-L*, anxiodepressive-like; *AMY*, amygdala; *BDI-II*, Beck Depression Inventory-II; *CCI*, chronic constriction injury; *CORT*, corticosteroids; *CRF*, corticotropin-releasing factor; *DHEA*, dehydroepiandrosterone; *PSNL*, partial sciatic nerve ligation; *TMD*, temporomandibular disorder

Table 9 Inflammatory factors and gliosis involved in neuropathic pain and concomitant anxiodepressive-like behaviors

	Expression	Species	Region	Models	Pain type	Mood disorder	Reference
Pro-inflammatory							
IL-1β	Increased	Rat	Liver	SNI	Neuropathic	D-L	Zhou et al. (2015)
	Increased	Mouse	Serum, cortex, HPC	PSNL	Neuropathic	D-L	Brüning et al. (2015)
	Increased	Rat	DH, HPC, PFC, NAc, AMY	SNI	Neuropathic	D-L	Gui et al. (2016)
	Increased	Mouse	HPC	CCI	Neuropathic	D-L	Kim et al. (2012)
	Increased	Rat	AMY	SNI, OB	Neuropathic	D-L	Burke et al. (2013a)
	Increased	Rat	HPC, cortex	Reserpine treatment	Hyperalgesia	D-L	Arora and Chopra (2013)
	Increased	Rat	HPC	SNI, MD	Neuropathic	D-L	Burke et al. (2013b)
	Increased	Mouse	Brain	CFA injection	Inflammatory	D-L	Maciel et al. (2013)
	Increased	Mouse	PFC	SNI	Neuropathic	D-L	Norman et al. (2010a, b)
	Increased	Mouse	PFC	PSNL	Neuropathic	A-L	González-Sepúlveda et al. (2016)
IL-6	Increased	Mouse	HPC	CCI	Neuropathic	D-L	Jiang et al. (2018)
	Increased	Rat	Plasma, HPC	CFA-injection	Inflammatory	D-L	Kim et al. (2012)
	Increased	Human	Plasma	Chronic back pain	Back pain	MDD	Kim et al. (2012)
	Decreased	Rat	AMY	SNI, OB	Neuropathic	D-L	Burke et al. (2013a)
	Increased	Mouse	Serum, cortex, HPC	PSNL	Neuropathic	D-L	Brüning et al. (2015)
TNF-α	Increased	Mouse	HPC	CCI	Neuropathic	D-L	Jiang et al. (2018)
	Increased	Mouse	Sciatic nerve, PFC, HPC	Peripheral nerve crush	Neuropathic	D-L	Nascimento et al. (2015)
	Increased	Rat	HPC, cortex	Reserpine treatment	Hyperalgesia	D-L	Arora and Chopra (2013)
	Increased	Rat	HPC	SNI, MD	Neuropathic	D-L	Burke et al. (2013b)
	Increased	Mouse	Frontal cortex	Reserpine treatment	Hyperalgesia	D-L	Xu et al. (2013)
	Increased	Mouse	Serum, cortex, HPC	PSNL	Neuropathic	D-L	Brüning et al. (2015)
TNF	increased	Mouse	HPC	CCI	Neuropathic	D-L	Dellarole et al. (2014)
Anti-inflammatory							
INF-γ	Increased	Mouse	Serum, cortex, HPC	PSNL	Neuropathic	D-L	Brüning et al. (2015)
IL-10	Decreased	Mouse	Serum, cortex, HPC	PSNL	Neuropathic	D-L	Brüning et al. (2015)
	Increased	Rat	AMY	SNI, OB	Neuropathic	D-L	Burke et al. (2013a)
Astrocytes							
GFAP	Increased	Rat	HPC	SNI, MD	Neuropathic	D-L	Burke et al. (2013b, 2015b)
	Increased	Mouse	PAG	SNI	Neuropathic	D-L	Norman et al. (2010b)
	Increased	Rat	AMY	SNI, OB	Neuropathic	D-L	Burke et al. (2013a)
Microglia							
CD11b	Increased	Rat	AMY	SNI, OB	Neuropathic	D-L	Burke et al. (2013a)
	Increased	Rat	HPC	SNL, OB	Neuropathic	D-L	Burke et al. 2015b
Other mechanisms							
NF-κβ	Increased	Rat	HPC, cortex	Reserpine treatment	Hyperalgesia	D-L	Arora and Chopra (2013)
	Increased	Mouse	HPC, cortex	PSNL	Neuropathic	D-L	Brüning et al. (2015)

A-L, anxiety-like; *AMY*, amygdala; *CCI*, chronic constriction injury; *CFA*, complete Freund's adjuvant; *DH*, dorsal horn; *D-L*, depressive-like; *GFAP*, glial fibrillary acidic protein; *HPC*, hippocampus; *IL-6*, interleukin 6; *IL-10*, interleukin 10; *IL-1β*, interleukin 1beta; *INF-γ*, interferon gamma; *MD*, maternal deprivation; *MDD*, major depressive disorder; *NAc*, nucleus accumbens; *NF-κβ*, nuclear factor-kappa beta; *OB*, olfactory bulbectomy; *PAG*, periaqueductal gray; *PFC*, prefrontal cortex; *PSNL*, partial sciatic nerve ligation; *SNI*, spared nerve injury; *SNL*, spinal nerve ligation; *TNF*, tumor necrosis factor; *TNF-a*, tumor necrosis factor alpha target for further in-depth studies and even potential new therapeutic options.

Neuroinflammatory factors

Neuroinflammatory alterations play an important role in the pathophysiology of depression (Capuron and Miller 2011; Dantzer et al. 2008) and chronic pain (Clark et al. 2013; Miller et al. 2009) as demonstrated by pre-clinical studies showing a sustained imbalance between pro-inflammatory and anti-inflammatory cytokines and alterations in immune and non-immune cells. During the last 10 years, an increasing number of studies focused on the involvement of these factors in the comorbidity of chronic pain and depression (Burke et al. 2015a). For instance, clinical studies showed that patients with chronic back pain (Kim et al. 2012) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (Hu et al. 2016) with comorbid depression had elevated plasma pro-inflammatory cytokines which initiate, orchestrate, and amplify the inflammatory response of IL-6, IL-1α, IL-1β, and TNF-α. Moreover, in the cerebrospinal fluid of patients with complex regional pain syndrome (CRPS), IL-1β and IL-6, but not TNF-α, were also found to be increased (Alexander et al. 2005).

Pre-clinical studies focusing on different chronic pain models with comorbid anxiety/depression reported upregulation of IL-6 in serum and cerebrospinal fluid in the CP/CPPS syndrome in the hippocampus and cortex, as well as in

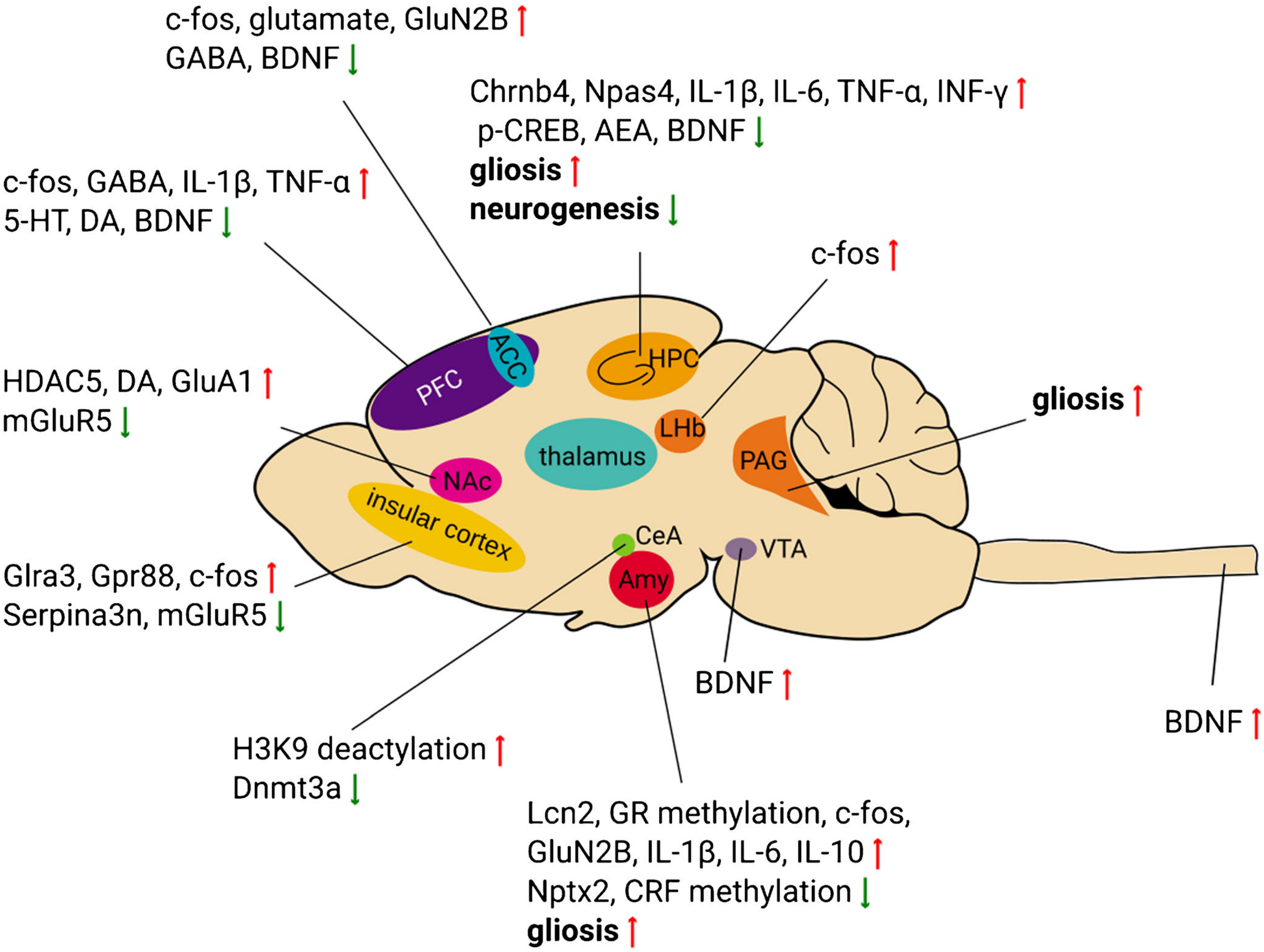

Fig. 1 Summary of molecular alterations involved in pre-clinical rodent models of comorbid chronic pain and anxiodepressive-like behaviors. Red up-arrows: increased level; green down-arrows: decreased level. 5-HT, serotonin; ACC, anterior cingulate cortex; AEA, anandamide; AMY, amygdala; BDNF, brain-derived neurotrophic factor; CeA, central amygdala; Chrnb4, cholinergic receptor nicotinic beta 4 subunit; CRF, corticotropin-releasing factor; DA, dopamine; Dnmt3a, DNA methyltransferase; GABA, gamma-aminobutyric acid; GALR2, galanin-2 receptor; Glra3, glycine receptor alpha 3; GluA1, AMPA receptor subunit; GluN2B, NMDA receptor 2B; Gpr88, G protein–coupled receptor 88; GR, glucocorticoid receptor; HDAC5, histone deacetylase 5; HPC, hippocampus; IL-6, interleukin 6; IL-10, interleukin 10; IL-1β, interleukin 1beta; INF-γ, interferon gamma; Lcn2, lipocalin-2; LHb, lateral habenula; Lmx1b, LIM homeobox transcription factor 1 beta; mGluR5, metabotropic glutamate receptor 5; NAc, nucleus accumbens; NF-κβ, nuclear factor-kappa beta; Npas4, neuronal PAS domain protein 4; Nptx2, neuronal pentraxin-2; PAG, periaqueductal gray; p-CREB, phospo c-AMP-response element binding; PFC, prefrontal cortex; Serpina3n, serpin peptidase inhibitor; TNF-α, tumor necrosis factor alpha; VTA, ventral tegmental area

inflammatory and neuropathic pain models (Kim et al. 2012; Jiang et al. 2018; Brüning et al. 2015). In contrast, the level of IL-6 was downregulated in the amygdala (Burke et al. 2013a). Using diverse neuropathic pain models in rodents, it has also been shown that the IL-1β expression was enhanced in the liver (Zhou et al. 2015), plasma (Brüning et al. 2015; Gui et al. 2016), spinal DH (Gui et al. 2016; Apkarian et al. 2006), PFC (Apkarian et al. 2006; Norman et al. 2010a, b; Arora et al. 2011; Arora and Chopra 2013; Brüning et al. 2015; González-Sepúlveda et al. 2016; Gui et al. 2016), hippocampus (Apkarian et al. 2006; Arora et al. 2011; del Rey et al. 2011; Kim et al. 2012; Arora and Chopra 2013; Burke et al. 2013b; Brüning et al. 2015; Gui et al. 2016), NAc (Gui et al. 2016), amygdala (Burke et al. 2013b; Gui et al. 2016), and brainstem. Another major pro-inflammatory cytokine, TNF-α, was also observed to be increased in the serum (Brüning et al. 2015), the PFC (Nascimento et al. 2015; Brüning et al. 2015), and the hippocampus (Jiang et al. 2018; Nascimento et al. 2015; Burke et al. 2013b; Brüning et al. 2015; Dellarole et al. 2014) in rodent models displaying comorbid neuropathic pain and anxiety/depression. On the other hand, anti-inflammatory cytokines' IL-10 and INF-γ levels were altered in the serum, cortex, hippocampus, and amygdala in neuropathic pain rat models (Brüning et al. 2015; Burke et al. 2013a).

In addition, glial cells like microglia and astrocytes also contribute to the cross talk between immune system and neural system. Microglia activation was observed in the amygdala (Burke et al. 2013a) and hippocampus (Burke et al. 2015b), while astrogliosis was reported in the hippocampus, amygdala, and PAG (Norman et al. 2010b; Burke et al. 2013a, b) of animals displaying anxiodepressive-like behaviors after neuropathic pain (see Table 9).

Conclusion and future directions

As seen from the studies presented in this review (see Fig. 1), the past 10 years have yielded a growing number of studies which tried to understand the molecular mechanisms of the comorbidity of chronic pain and mood disorders. While clinical studies provide genetic data, pre-clinical studies were crucial for divulging cause-effect relations. However, overall, our understanding of the mechanisms underlying the development of chronic pain and mood disorders such as depression remains strikingly limited. Although the recent advances highlight various aspects of brain anatomy and physiology which seem to play an important role in the process, detailed cellular and molecular contributions to the transition to chronic pain–depression comorbidity are not available. One way to get closer to this would be to have a more systemic approach while analyzing animal models, where each model is interpreted as a condition for itself. In fact, different characteristics of a specific model such as species (i.e., mouse, rat), strain, age, sex, type, and duration of pain or stress should all be taken into account when analyzing the molecular and physiological phenotype. It is very certain that different combinations of these characteristics might produce very different, if not opposite, results at the molecular, cellular, and behavioral level. It is thus necessary to make side-by-side comparison of data ranging from molecular to behavioral changes obtained from different animal models. Indeed, a detailed characterization of different models displaying a comorbidity of pain and mood disorders would allow clarifying the temporal development of phenotypic changes at different levels, hence shedding light on the order in which certain molecular, cellular, and behavioral alterations manifest in these conditions. Once this is established and clarified, one of the important questions which needs to be further analyzed is whether the chronic pain and mood/anxiety disorders share similar neural mechanisms or chronic pain modulates neural mechanisms which increase the vulnerability for mood/anxiety disorders. As highlighted in this review, the comorbidity can be explained by shared molecular mechanisms observed in both chronic pain and mood disorders such as polymorphisms of 5-HT transporter and imbalance of inhibitory and excitatory neurotransmission or pro-inflammatory and anti-inflammatory cytokines. However, further clinical and pre-clinical studies are still needed to examine the second hypothesis and to search for indicative biomarkers in order to identify candidates for early diagnosis of developing comorbidity of chronic pain and mood disorders. Finally, forthcoming efforts devoted to exposing the underlying molecular mechanisms of chronic pain and depression should direct to novel therapeutic advancements for prevention and alleviation of the negative consequences of these conditions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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