



Review

Analgesic Mechanisms of Antidepressants for Neuropathic Pain

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Received: 22 October 2017; Accepted: 19 November 2017; Published: 21 November 2017

Abstract: Tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors are used to treat chronic pain, such as neuropathic pain. Why antidepressants are effective for treatment of neuropathic pain and the precise mechanisms underlying their effects, however, remain unclear. The inhibitory effects of these antidepressants for neuropathic pain manifest more quickly than their antidepressive effects, suggesting different modes of action. Recent studies of animal models of neuropathic pain revealed that noradrenaline is extremely important for the inhibition of neuropathic pain. First, increasing noradrenaline in the spinal cord by reuptake inhibition directly inhibits neuropathic pain through α_2 -adrenergic receptors. Second, increasing noradrenaline acts on the locus coeruleus and improves the function of an impaired descending noradrenergic inhibitory system. Serotonin and dopamine may reinforce the noradrenergic effects to inhibit neuropathic pain. The mechanisms of neuropathic pain inhibition by antidepressants based mainly on experimental findings from animal models of neuropathic pain are discussed in this review.

Keywords: noradrenaline; 5-HT; dopamine; spinal cord; α_2 -adrenergic receptors; locus coeruleus; spinal nerve ligation; hyperalgesia; allodynia; rats

1. Introduction

Although antidepressants were not originally designed to act as analgesics, they are reported to have analgesic effects for chronic pain. Antidepressants have virtually no antinociceptive effects, but are considered first-line drugs of choice for neuropathic pain [1–4] and treatment of fibromyalgia [5]. Specific antidepressants with analgesic effects include tricyclic antidepressants (TCA), which have long been used, and serotonin noradrenaline reuptake inhibitors (SNRI), which are comparatively new antidepressants. Selective serotonin reuptake inhibitors (SSRI), which are frequently used to treat depression, are not effective against chronic pain [1–3].

2. Effects of Antidepressants on Neuropathic Pain Differ from Their Effects on Depression

Antidepressants, along with pregabalin/gabapentin (voltage-dependent calcium channels $\alpha_2\delta$ subunit ligands) are used as first-line drugs for treating neuropathic pain [1–4]. Psychologic problems play an important role in chronic pain. Protracted pain causes anxiety accompanied by a progressive depressive state and enhanced pain sensations. Therefore, antidepressant medications may be effective against chronic pain by their effects to improve the depressive state. Antidepressants inhibit neuropathic pain, however, even when the patient is not in a depressive state [6]. In addition, the effects of antidepressants on depression characteristically take approximately two to four weeks to be observed from the time the drug is first taken, whereas the analgesic effects on chronic pain manifest in as little as few days to one week [7]. Therefore, the analgesic effects of antidepressants on chronic pain likely involve a mechanism different from that mediating their antidepressive effects.

3. Noradrenaline Is Extremely Important for Inhibiting Neuropathic Pain

The pharmacologic effects of antidepressants involve binding to noradrenaline and serotonin (5-HT) transporters. Reuptake of these neurotransmitters is inhibited, leading to increased levels of noradrenaline and 5-HT in the synaptic cleft [8–11]. What type of antidepressants is most effective against neuropathic pain? The “number needed to treat” (NNT) is an index used to compare the efficacy of medications based on the results obtained in a variety of clinical studies (meta analysis) and is represented as the number of patients treated for whom pain was reduced by up to 50%, with a smaller numerical value indicating a stronger efficacy [12,13]. According to a report from Finnerup et al., the NNT of TCA to inhibit peripheral neuropathic pain is approximately 2–3. The NNT of dual-type TCAs (e.g., amitriptyline, imipramine, clomipramine), which inhibit reuptake of both noradrenaline and 5-HT, is 2.1. The NNT for noradrenaline reuptake inhibitors (nortriptyline, desipramine) is approximately 2.5 [14]. The NNT for SNRI is 5.0 and for SSRI is 6.8 in painful polyneuropathy [2]. Based on these results, an antidepressant that inhibits reuptake of both noradrenaline and 5-HT has stronger analgesic effects than a drug that selectively inhibits reuptake of only one of these neurotransmitters, and noradrenaline plays a greater role than 5-HT in the analgesic action.

4. Noradrenaline Inhibits Neuropathic Pain in the Spinal Cord

Noradrenaline reuptake inhibition enhances analgesic effects, mainly through α_2 -adrenergic receptors in the dorsal horn of the spinal cord. The α_2 -adrenergic receptors are coupled to the inhibitory G protein (Gi/o), which inhibits the presynaptic voltage-gated Ca^{2+} channels in the dorsal horn of the spinal cord that inhibits the release of excitatory neurotransmitters from primary afferent fibers. At the same time, G protein-coupled inwardly rectifying K^+ channels are opened on the post-synaptic spinal cord dorsal horn cells, the cell membranes are hyperpolarized, and excitability is decreased [15]. While activation of the α_2 -adrenergic receptors of the spinal cord dorsal horn has weak antinociceptive effects against noxious stimuli, extensive research indicates that it is extremely effective against allodynia and hyperalgesia associated with neuropathic pain [16,17]. The reason for the increasing efficacy for hypersensitivity of spinal α_2 -adrenergic receptors stimulation is that nerve injury changes the function of α_2 -adrenergic receptors in the dorsal horn of the spinal cord [18,19], while at the same time the interaction with the cholinergic interneurons strengthens [20–23]. Our findings support the importance of α_2 -adrenergic receptors in the spinal cord dorsal horn for the inhibition of neuropathic pain. We used a rat model of neuropathic pain known as spinal nerve ligation (SNL). In this procedure, the L5 spinal nerve is ligated on one side [24]. When mechanical pressure is applied to the ipsilateral hind paw on the ligated side using a paw-pressure test, the withdrawal threshold decreases and mechanical hyperalgesia develops. Intrathecal administration of an α_2 -adrenergic receptor agonist, dexmedetomidine, leads to the release of acetylcholine to the spinal cord and mechanical hyperalgesia is inhibited through the muscarinic receptors [16]. In animals with nerve injury, the α_2 -adrenergic receptors expressed in the cholinergic interneurons of the spinal cord dorsal horn are coupled with excitatory G protein (G_S) by the action of brain-derived neurotrophic factor (BDNF) through TrkB receptor and acetylcholine is released by stimulation of the α_2 adrenergic receptors [23]. As a result, muscarinic receptors, which induce gamma-aminobutyric acid (GABA) release [25,26], contribute to the inhibitory effects of α_2 -adrenergic receptor activation for neuropathic pain (Figure 1). Thus, the pain relief mediated by noradrenaline in the dorsal horn of the spinal cord is more effective for neuropathic pain than for nociceptive pain due to plastic changes of the α_2 -adrenergic receptors.

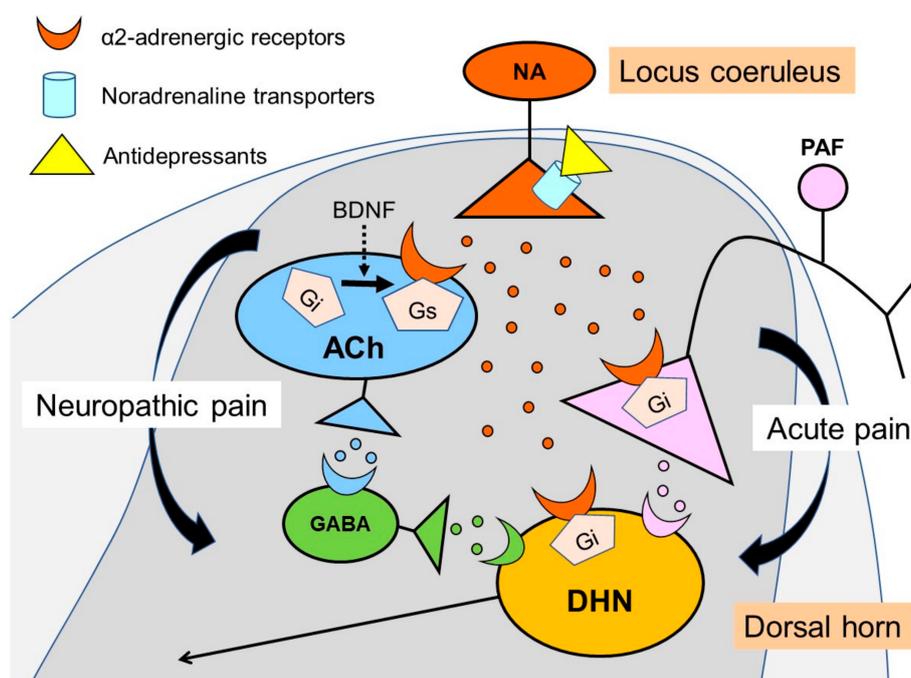


Figure 1. Schematic illustration of analgesic effects of antidepressants and noradrenaline in the dorsal horn of the spinal cord. Antidepressants increase noradrenaline via blocking of noradrenaline transporters at the terminal of the descending noradrenergic fiber from the locus coeruleus. Noradrenaline inhibits acute pain through α_2 -adrenergic receptors by pre-synaptic (inhibit neurotransmitters release) and post-synaptic (hyperpolarize cell membranes) mechanisms. In neuropathic pain states, however, α_2 -adrenergic receptors in the cholinergic interneurons change from inhibitory to excitatory through G-protein switch (from Gi to Gs) by the effect of brain-derived neurotrophic factor (BDNF) increasing after nerve injury. Released acetylcholine bind to muscarinic receptors, by which produce analgesia thorough GABA release. PAF; primary afferent fibers, NA; noradrenaline, DHN; dorsal horn neurons, ACh; acetylcholine, Red circle; noradrenaline, Blue circle; acetylcholine, Green circle; GABA, Pink circle; excitatory neurotransmitters.

Intraperitoneal administration of duloxetine, an SNRI, to SNL rats increases the withdrawal threshold for at least 4 h, but the effect disappears after 24 h. When duloxetine is administered for three consecutive days, the withdrawal threshold gradually increases and returns to pre-SNL levels. This increase in the withdrawal threshold is reversed by intrathecal injection of idazoxan, an α_2 adrenergic receptor antagonist, and the amount of noradrenaline in the dorsal horn of the spinal cord increases after three daily injections of duloxetine [27] (Figure 2). In addition, in animals pretreated with a noradrenergic neurotoxin (DSP-4), the antihyperalgesic effect of duloxetine is weakened [28]. Intraperitoneal administration of amitriptyline, a TCA, over consecutive days gradually increases the withdrawal threshold, but this antihyperalgesic effect is reversed by intrathecal injection of an α_2 -adrenergic antagonist [28].

Noradrenaline in the dorsal horn of the spinal cord is increased by a single intraperitoneal injection of antidepressants such as amitriptyline (TCA), duloxetine and milnacipran (SNRI), or fluoxetine and paroxetine (SSRI) (Figure 3). In addition, a single administration of paroxetine produces an anti-hyperalgesic effect, which is inhibited by intrathecal injection of an α_2 -adrenergic receptor antagonist [29] Fluoxetine and paroxetine have weak inhibitory effects on noradrenaline transporters [30,31], and thus their effects to increase noradrenaline are likely indirect. These findings suggest that the increase in noradrenaline in the spinal cord plays a crucial role in the inhibitory effects of antidepressants on neuropathic pain.

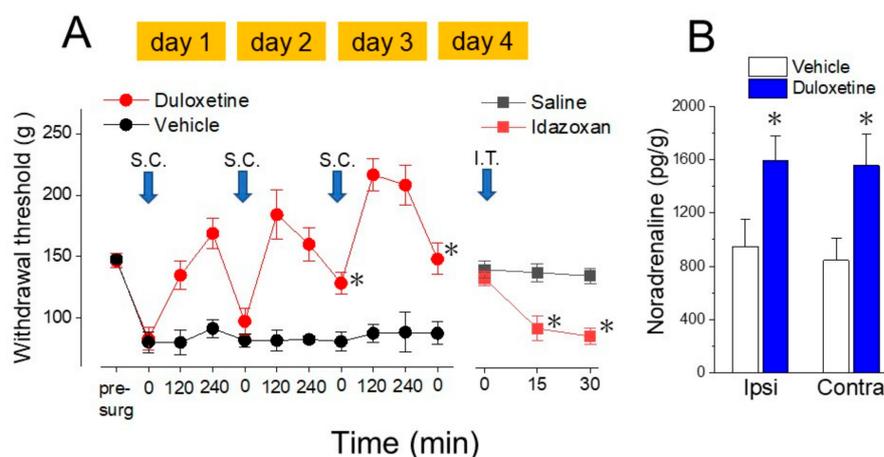


Figure 2. Antihyperalgesic effects of duloxetine in rats after nerve injury by noradrenaline increase in the spinal cord. (A) Effects of three daily injections of duloxetine on hind paw mechanical hyperalgesia after spinal nerve ligation (SNL) in rats. Rats were administered duloxetine (10 mg/kg/day, subcutaneous injection) or vehicle for three consecutive days. Each day, withdrawal thresholds in ipsilateral hind paw were measured at time 0 (baseline: before each duloxetine injection), and 120 and 240 min after the injection. Three daily treatment increased baseline withdrawal thresholds (time 0) of on days 3 and 4 than on day 1 (* $p < 0.05$ compared with the duloxetine group at time 0 on day 1). Acute antihyperalgesic effects until 240 min after injection were also observed. Then, rats were injected intrathecally (i.t.) with idazoxan, an α_2 -adrenoceptor antagonist (30 $\mu\text{g}/20 \mu\text{L}$) or vehicle. The injection of idazoxan reversed the antihyperalgesic effect of duloxetine (* $p < 0.05$ compared with the vehicle group at each time-point). (B) Spinal cord tissue from SNL rats injected with duloxetine (10 mg/kg/day) or vehicle for three consecutive days was homogenized, and the noradrenaline content was measured. Noradrenaline was increased with duloxetine treatment at both ipsilateral and contralateral to the SNL compared to the vehicle group (* $p < 0.05$). Data in this figure published from Ref. [27].

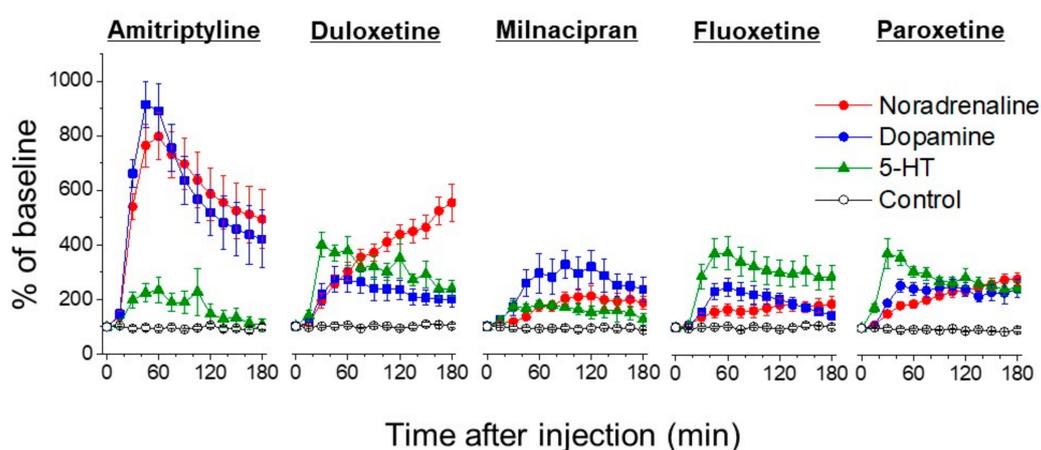


Figure 3. Percentage changes of noradrenaline, dopamine, and 5-HT levels in the dorsal horn of the lumbar spinal cord in rats after intraperitoneal injection of 10 mg/kg of amitriptyline (TCA), duloxetine (SNRI), milnacipran (SNRI), fluoxetine (SSRI) and Paroxetine (SSRI). Under isoflurane anesthesia, microdialysis studies were performed after thoracolumbar laminectomy, and monoamines were measured by using high-performance liquid chromatography with electrochemical detection. All monoamines were increased after injection of all antidepressants (all $p < 0.05$ compared to control; saline or vehicle, by two-way repeated-measures analysis of variance. Some data in this figure published from Ref. [32]).

5. Actions of Antidepressants on the Locus Coeruleus

The locus coeruleus (LC) comprises a group of nerve cells containing noradrenaline located bilaterally in the brain. The LC has the greatest amount of noradrenaline in the central nervous system and is located on the right and left of the posterior brainstem facing the fourth ventricle [33,34]. Noradrenergic nerve fibers project virtually throughout the entire central nervous system and play a role in sleep, wakefulness, cognition, learning and stress in the brain [35–37]. In the spinal cord, noradrenergic nerve fibers regulate endogenous analgesia, posture and motion, the autonomous nervous system, and other vital functions [38–40]. The neuronal activity of the LC is characterized by a tonic (autonomous activity) mode and a phasic (activity that reacts to stimulus) mode. Phasic activity is an excitatory reaction within a short period of time in which stimuli induce the release of an excitatory amino acid (mainly glutamic acid) in the LC. Phasic activity during the tonic activity mode at a medium level from a lower level plays an important role in attention, movement and concentration on outside stimuli, such as cognitive functions, endogenous analgesia and a variety of other vital functions [35,41]. Descending noradrenergic neurons are an extremely important mechanism of endogenous analgesia. In rats, the bilateral LC is excited phasically by noxious stimulation, and releases noradrenaline through projections to the bilateral spinal cord dorsal horn [38,41,42].

How does the activity of the descending noradrenergic inhibitory system from the LC change in a neuropathic pain state? Noxious stimulation induced analgesia (NSIA) is an animal model in which the intensity of endogenous analgesia can be measured. The withdrawal threshold in response to the mechanical stimulus on the hind paw greatly increases after forepaw capsaicin injection by activation of the endogenous analgesia [43]. An increase in noradrenaline in the spinal cord affects the NSIA [41,43,44]. This means that the LC is activated phasically due to the pain induced by the capsaicin, and the noradrenaline that is released to the spinal cord mediates antinociceptive effects through α_2 -adrenergic receptors. When the same experiment was carried out using animal models of neuropathic pain (SNL animals), the NSIA was no longer recognized six weeks after nerve injury (an increase in the withdrawal threshold of the hind paw no longer occurred when capsaicin was administered to the forepaw), and the noradrenaline is not increased in the spinal cord [27,41,44]. At this time, the tonic nerve activity of the LC increased due to nerve injury, but the phasic reactivity to the noxious stimuli disappeared [41]. Based on these results, the phasic activity of the neuronal cells of the LC gradually declined in the neuropathic pain model after a long period of time had passed from the nerve injury, and the descending noradrenergic inhibitory system was impaired.

In animals with nerve injury and impaired NSIA, administering duloxetine and amitriptyline over several consecutive days recovers the NSIA [27,44]. Although the increase in noradrenaline in the spinal cord induced by these antidepressants plays a part in the NSIA recovery, it is possible that the effect of the drugs on the LC contributed to the effect. The LC receives inputs from a variety of sites of the central nervous system and its activity is controlled by both noradrenaline and 5-HT [45]. Antidepressants increase noradrenaline around the LC [46], and inhibit the activity of the LC through α_2 -adrenergic receptors [47,48]. In contrast, another report suggests that when duloxetine and desipramine are administered consecutively, the increased noradrenaline desensitizes the α_2 -adrenergic receptors in the LC [49]. In animal models of neuropathic pain, the reaction of the LC to noxious stimuli differs from that in normal animals due to sensitization via *N*-methyl-D-aspartic acid (NMDA) receptors, but this report indicates that the reaction is normalized by the consecutive administration of duloxetine and desipramine [49].

Furthermore, a previous study demonstrated that nerve injury increases the basal extracellular glutamate concentration in the LC [41], which may reduce noxious stimulation-evoked glutamate release, thereby diminishing α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated LC activation, which is important for inducing NSIA. Another previous study demonstrated that antidepressants increased BDNF levels in astrocyte cultures [50]. BDNF triggers AMPA receptor GluA1 phosphorylation and regulates trafficking of the AMPA receptor to the cell

membrane [51]. Therefore, antidepressants may reactivate impaired LC function after nerve injury by increasing BDNF levels.

6. The Role of 5-HT

Many antidepressants block 5-HT transporters, leading to increased 5-HT in the synaptic cleft. The role of 5-HT on the inhibitory effects of antidepressants against neuropathic pain, however, is unclear. Although SSRIs are popular drugs for the treatment of depression, they are not recommended for the treatment of neuropathic pain [1–3]. Despite some reports of their effectiveness in randomized controlled trials in patients with chronic pain, the NNT for SSRIs is higher than that for TCA and SNRI [2,14]. For this reason, 5-HT is thought to play a less important role than noradrenaline in the inhibition of neuropathic pain, but simultaneous administration of noradrenaline and 5-HT selective reuptake inhibitors in an animal experiment produce a synergistic analgesic effect [52], suggesting that 5-HT has auxiliary actions.

5-HT in the dorsal horn of the spinal cord greatly contributes to pain modulation. Inhibitory 5-HT_{1A} receptors, and excitatory 5-HT_{2A/2C}, 5-HT₃, and 5-HT₇ receptors that strongly contribute to nociceptive transmission are expressed in the dorsal horn of the spinal cord [53–56]. These receptors are present in the pre-synaptic terminals of primary afferent nerve fibers, inhibitory interneurons, excitatory interneurons and projection neurons, and modify nociceptive transmission. When the pain sensation reaches the brain, the descending inhibitory system is mobilized from a variety of sites in the cerebral cortex and activates the periaqueductal gray (PAG) [56,57]. The PAG closely controls the rostroventromedial medulla (RVM) and modifies pain via projecting fibers from the RVM to the dorsal horn of the spinal cord [56–58]. The RVM includes the nucleus raphe magnus, which projects abundant serotonergic fibers to the spinal cord dorsal horn [58]. Descending serotonergic projections from the RVM to the spinal cord dorsal horn exert both inhibitory and facilitatory effects on pain processing depending on the pain state, acute or chronic [58–60]. In neuropathic pain models, many studies reported that ablation of descending 5-HT pathways inhibit pain hypersensitivity [61–63], and have also demonstrated that nerve injury induces descending facilitation by activating spinal 5-HT₃ receptors [64,65]. Activation of descending serotonergic neurons from the RVM is required, however, for this descending facilitation to occur. In contrast, direct intrathecal injection of 5-HT or a 5-HT₃ agonist inhibits allodynia in a rat neuropathic pain model [66,67]. Systemic administration of paroxetine, an SSRI, produces an anti-hyperalgesic effect in a rat model of neuropathic pain through spinal 5-HT₃ receptors [29], because the drug directly increases 5-HT in the spinal cord by inhibiting 5-HT transporters.

Several lines of evidence suggest that 5-HT receptor function changes in neuropathic pain states. Although 5-HT_{2A} receptors in the spinal cord dorsal horn contribute to the suppression of neuropathic pain [68–70], the inhibitory effects of systemically administered SSRIs on hyperalgesia after nerve injury are stronger when spinal 5-HT_{2A} receptors are disrupted from their associated PDZ proteins by intrathecal injection of a peptide (TAT-2ASCV) [71]. Systemic administration of a 5-HT_{1A} receptor agonist (NLX-112) strongly inhibits inflammatory pain, but is less effective against neuropathic pain [72].

Thus, there are many reports suggesting a less important role for 5-HT in inhibition of neuropathic pain compared to acute pain. Increased 5-HT in the spinal cord by antidepressants may, however, play some inhibitory role for neuropathic pain.

7. The Role of Dopamine

Descending dopaminergic neurons, which project from the mesolimbic A11 dopamine cell group to the spinal cord dorsal horn, release dopamine in the dorsal horn of the spinal cord and inhibit nociceptive transmission by mediating dopamine D2-like receptors [73,74]. Bupropion, a dopamine noradrenaline reuptake inhibitor, increases noradrenaline and dopamine levels in the spinal cord and suppresses hyperalgesia in a rat neuropathic pain model through α_2 -adrenergic receptors and

D2-like receptors [75]. No other antidepressants are reported to strongly inhibit dopamine transporters. Nevertheless, we demonstrated that intraperitoneal administration of amitriptyline (TCA), duloxetine and milnacipran (SNRI) and fluoxetine (SSRI) at a dose of 10 mg/kg, all increased dopamine in the spinal cord and inhibited hyperalgesia in a rat model of neuropathic pain through D2-like receptors [32]. There are few dopamine transporters in the frontal cortex and reuptake of dopamine is mediated by noradrenaline transporters [76]. It is unclear why antidepressants increase dopamine levels in the spinal cord.

Dopaminergic neurons in the ventral tegmental area (A10) release dopamine in the nucleus accumbens and enhance analgesic activity through D2-like receptors [77–79]. A previous study demonstrated that duloxetine (25 mg/kg orally) increases dopamine in the nucleus accumbens, but amitriptyline and maprotiline (both 50 mg/kg orally) do not have this effect [80]. Dopamine enhances the antinociceptive effects in the striatum [81,82]. Although it is unclear whether antidepressants increase dopamine in these brain areas, dopamine increases in the central nervous system are likely to play a role in the inhibitory effect of antidepressants on neuropathic pain.

8. Other Actions

Antidepressants have a number of other actions in addition to increasing monoamines that may contribute to the inhibition of neuropathic pain. First, they act as sodium channel blockers [83,84]. Sodium channel blockers inhibit ectopic discharges occurring when there is nerve damage, thereby inhibiting neuropathic pain [85,86]. Second, some antidepressants act as NMDA receptor antagonists [87,88]. NMDA receptors, which are expressed in the neurons of the dorsal horn of the spinal cord, induce wind-up and central sensitization result in contribute to the onset and maintenance of neuropathic pain [89,90].

TCAs also act as α_1 -adrenergic receptors [91], calcium channel blockers [92], potassium channel activators [93], modulate the adenosine system [94] and increase GABA-B receptor function [95]. They activate opioid receptors [96], inhibit the production of nitric oxide, prostaglandin E2 [97] and have a variety of other actions that may inhibit neuropathic pain in a complex manner.

9. Conclusions

The main mechanism of antidepressants that inhibit neuropathic pain is first, to increase noradrenaline in the spinal cord, and second, to act on the LC, thereby directly inhibiting pain and activating the impaired descending noradrenergic inhibitory system. Dopamine and 5-HT also increase in the central nervous system and may enhance the inhibitory effects of noradrenaline in an auxiliary manner.

Conflicts of Interest: The authors declare no conflict of interest.

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