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REVIEW

Diabetic Neuropathic Pain and Circadian Rhythm: A Future Direction Worthy of Study

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Abstract: More than half of people with diabetes experience neuropathic pain. Previous research has shown that diabetes patients' neuropathic pain exhibits a circadian cycle, which is characterized by increased pain sensitivity at night. Additional clinical research has revealed that the standard opioid drugs are ineffective at relieving pain and do not change the circadian rhythm. This article describes diabetic neuropathic pain and circadian rhythms separately, with a comprehensive focus on circadian rhythms. It is hoped that this characteristic of diabetic neuropathic pain can be utilized in the future to obtain more effective treatments for it.

Keywords: diabetic neuropathies, circadian rhythm, pain, chronotherapy, microglia, sex characteristics

Introduction

In 2011, the International Association for the Study of Pain defined neuropathic pain (NP) as "pain caused by injury or disease of the somatosensory system"[1] An increasing amount of research conducted in the last several years has demonstrated a close relationship between neuropathic pain and the brain and spinal cord's functioning.[2] Neuropathic pain can be brought on by tumors, injuries, inflammation, and neurological conditions such as peripheral neuropathy brought on by diabetes.[3] Nociceptive hypersensitivity and spontaneous pain are two characteristics of neuropathic pain, which is a frequent side effect of numerous illnesses.[4]

Diabetes affects approximately 9% of people worldwide in 2019 and will continue to affect a far larger percentage.[5] Around 15% to 25% of patients with diabetes experienced neuropathic pain or painful DPN.[6,7] A range of symptoms, primarily in the lower body, such as burning, cramping, and sinking sensations, along with depressive symptoms, are indicative of DNP.[8] Diabetic neuropathy is a degenerative condition whose symptoms get worse with time.[6] Nerve pain, either continuous or sporadic, is experienced by one-third of diabetic peripheral neuropathy patients. Pain typically manifests in the early stages of neurotoxicity following diagnosis or before diabetic management.[9]

At the moment, DNPs are mostly utilized by opioids, topical medications like capsaicin, antidepressants, and analogs of gamma-aminobutyric acid (GABA).[10] Despite several therapy approaches, only a very small percentage of individuals receive sufficient pain alleviation. Satisfaction with the treatment of circadian rhythm phenomena in DNP was also low. Furthermore, other potential pathways for pain resulting from diabetic peripheral neuropathy have been recognized, including increased levels of protein kinase C and auto-oxidative stress.[10] Even though the underlying pathophysiological mechanisms of DNP have been greatly expanded upon over the years of research, precise molecular and cellular pathways have remained elusive.[11]

Circadian rhythms are seen in almost all biological systems. These rhythms are natural and last for around a day. They are synchronized with the environment's light/dark cycle.[12] For instance, body temperature peaks and troughs occur around 16:00 and dawn, respectively; blood pressure is often greater at noon, and people experience increased fatigue around midnight. Pharmacological timing of medication delivery, or chronotherapy, is a significant medical innovation

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that resulted from an understanding of the fundamental circadian function of biological organisms. For instance, starting the prescribed antihypertensive and asthma medications before the peak arterial systolic blood pressure and lung function drop, respectively.[13,14]

The supraoptic nucleus (SCN), sometimes referred to as the central pacemaker, is principally responsible for regulating the circadian rhythms of practically all mammals.[15] Numerous internal rhythms of the body are regulated by central pacemakers, such as melatonin and locomotor activity (LMA), eating, aggressiveness, body temperature, wake-sleep cycles, and corticosteroid secretion.[16,17] The central pacemaker was found to have a significant influence on animals' circadian rhythms in research conducted on rodents.[18–20] Through a variety of signals, the central pacemaker regulates the organism's biological clock.[21] Circadian rhythm oscillations are also present in a large number of cells, both central and peripheral.[22] Furthermore, none of the biological rhythms were present after the removal of the central pacemaker.[12]

The liver, brain, and lungs are among the organs that have been shown to exhibit circadian rhythms when isolated in vitro.[23] Cells that create transcription-translation feedback loops have been found to harbor a set of clock genes, also referred to as "clock-control genes".[24] These genes have distinct circadian phase distributions in various tissues and are tissue-specific.[25,26] About half of the mouse genes that code for proteins showed transcription that was characterized by circadian rhythms in an organ-specific way, and transcription of these genes peaked right before dusk or dawn.[27]

This phenomenon of the presence of circadian rhythms in neuropathic pain has been identified in several animal experiments and clinical studies, and this paper will compile these findings with the expectation of finding ways to utilize circadian rhythms to alleviate diabetic neuropathic pain.

Main Body

Diabetic Neuropathic Pain

DNP is one of the most common chronic complications caused by diabetes. This pain is mainly due to the long-term hyperglycemic state of diabetic patients, which leads to pathological changes in the peripheral nerve endings, resulting in discomfort such as burning, pins and needles, distension, etc. In some patients, it may also be accompanied by reduced skin sensation, sensory abnormalities, or nociceptive sensitization. Neuropathic pain due to diabetes mellitus has become a common clinical problem that requires further investigation into its pathogenesis and treatment.

The Pathogenesis of DNP

Diabetes-related neuropathic pain is associated with several risk factors, including age over 60, alcoholism, and smoking.[28] Increases or decreases in heat or cold sensitivity due to variations in the DNP's temperature-specific nerve fiber count.[29] Numerous elements interact to cause pain, which sets off a chain reaction of reactions.

Previous research has suggested that DNP may be linked to sensory neuron degeneration and synaptic stimulation of peripheral nerve fibers.[30,31] Subsequent research has also found a connection between pain and nerve regeneration markers in the skin. It's interesting to note that a diabetic patient who had both of his feet amputated experienced symmetrical discomfort in one research, indicating that pain does not always correspond to its source.[32] This opinion is supported by imaging investigations, which show that central and spinal cord dysfunction develops gradually as the disease progresses, starting from peripheral nerve fibers and moving toward the center.[33–35] As a result, DNP may develop over time due to changes at several loci.[35]

Patients with diabetic neuropathic pain had similar levels of glutathione and catalase, indicating that DNP may be partially caused by oxidative stress triggered by the polyol pathway.[10,36] Research indicates that DNP may be related to lower insulin levels.[37] The most often utilized model of diabetic neuropathy at the moment is diabetic rats produced with streptozotocin (STZ).[38] High dosages of STZ were used to produce nociceptive hypersensitivity more easily and dramatically decrease insulin production in diabetic rats.[39]

In the prodromal diabetes model, pain started to manifest before hyperglycemia but at the same time as insulin resistance.[40] The aforementioned diabetes model would exhibit quite different effects, including slower nerve fiber conduction and higher nociceptive sensitivity if it were administered with tiny quantities of insulin for more than a year.[41]

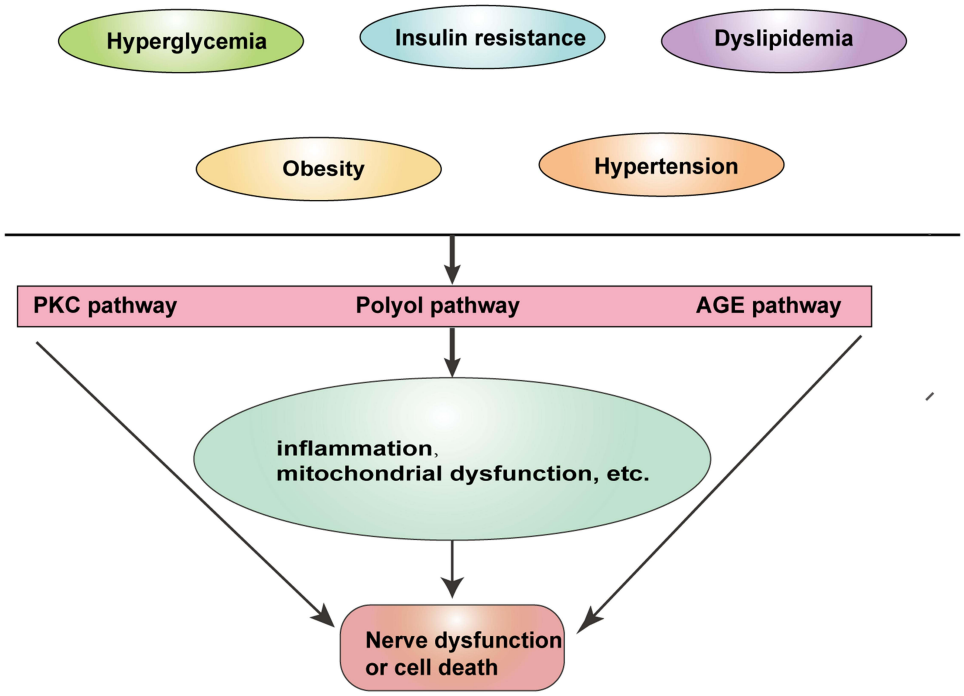

Figure 1 Factors associated with the pathogenesis of diabetic neuropathy. Hyperglycemia, dyslipidemia, and insulin resistance promote the activation of PKC, polyol, and AGE pathways, which ultimately affect mitochondrial function and lead to inflammation.

Nearly 1000 proteins have been linked to neuropathic pain in studies of the molecular pathways underlying the condition.[42] These proteins, which include NOS1, P2RX4, IL-6, MAPK14, and others, are interlinked and interact with one another to form a complex network. A genome-wide association analysis revealed additional gender disparities in diabetic neuropathic pain, with males having twice the heritability of females, and genetic variables associated with diabetic neuropathic pain were found.[43] A brief pathogenesis is shown in Figure 1.

Treatment of DNP

The prevailing method for managing diabetic neuropathic pain currently involves either a single medication or a combination of medications, such as pregabalin and duloxetine.[36] Pregabalin exerts its analgesic effect by binding to voltage-gated calcium channels and reducing the release of glutamate, norepinephrine, and substance P. Duloxetine, on the other hand, is an antidepressant that works by inhibiting the uptake of 5-hydroxytryptophan and norepinephrine. Unfortunately, none of these medications work as well as they should, as less than 50% of patients who take them report feeling better from their pain, and their negative side effects—such as exhaustion and dizziness—further restrict how often they can be used.[44] Consequently, the combination of first-line medications aids in the hunt for novel therapies that enhance the capacity of medications to relieve pain while boosting their specificity to lessen adverse effects.[45,46]

When medications are used in combination, there are several ways that pain might be reduced. For example, pregabalin has been shown to be efficacious in certain patients with DNP when used in combination with monoamine oxidase reuptake inhibitors.[47] Due to the lack of effectiveness of clinical drugs, opioids have come back into the picture. Opioids will be permitted for use in patients with diabetic neuropathic pain that cannot be controlled by first-line treatment combinations, despite their evident addictive qualities and propensity to demand higher dosages of medication.[45,48,49]

It has been discovered that topical administration completely avoids the negative effects connected with systemic therapy in the effort to treat diabetic neuropathic pain. Topical application of capsaicin cream was reported to decrease substance P in nerve fibers in a clinical investigation including almost three hundred participants. This, in turn, reduced neuropathic pain in diabetic patients.[50] In an animal pain model, capsaicin magnetic nanoparticles were found to reduce pain.[51] Co-administration of capsaicin and sodium channel blockers has been found to provide long-lasting relief from neuropathic pain.[52]

In a clinical experiment, topical isosorbide nitrate treatment was also observed to alleviate diabetic neuropathic pain in certain individuals.[53] Analgesic injections administered locally may alleviate neuropathic pain, but their inherent toxicity restricts their application.[10] Ion channels have been identified as a possible therapeutic target for the relief of neuropathic pain. A topical patch containing the sodium channel inhibitor lidocaine can be utilized to reduce pain by preventing the propagation of action potentials during pain.[47,54] Local administration has drawbacks though, and patients receiving medication locally tend to be less obedient. This is not because of the medication itself, but rather because local administration is more inevitable with this kind of administration, making it less effective than systemic administration.[55] The corresponding number of administrations rises, and some delicate bodily parts are at risk of contamination.[10]

Therefore, to get around the problems with the conventional method of drug distribution, a new one is required. Creating nanocarriers by combining polyesters and liposomes with some conventional analgesics, such as morphine, can increase their effectiveness and lessen their negative effects.[56] Several treatments for diabetic neuropathic pain are shown in Table 1.

Circadian Rhythm

From bacteria to plants to animals, organisms have a 24-hour timer called the circadian rhythm.[71] In the course of biological evolution, circadian rhythms have adapted to geophysical cycles and natural environmental cycles, and have formed a very complex regulatory mechanism within organisms.[72] As a central pacemaker, the SCN regulates circadian rhythms in mammals through neural signals or hormonal signals.[22] The SCN also regulates the circadian secretion of endocrine signals such as melatonin in the pineal gland and glucocorticoids and catecholamines in the adrenal cortex by modulating the hypothalamic-pituitary-adrenal axis.[73] Melatonin enhances nociceptive sensitivity, with increased secretion at 21:00 each day and a peak at 3:00 a.m. This may be related to the fact that diabetic neuropathic pain patients have more pain at night.[74] This may be related to the fact that diabetic neuropathic pain patients have more pain at night. The glucocorticoid cortisol peaks at 8 a.m. and may be associated with daytime pain patterns.[75] At the molecular level, the control of circadian rhythms relies on clock genes such as BMAL1, CLOCK, and NPAS2, which are highly conserved and form cell-autonomous transcriptional-translational autoregulatory feedback loops.[76]

Circadian rhythm disruption is prevalent in contemporary populations in all countries.[77] Nighttime light, jet lag, and disordered eating all have an impact on human circadian rhythms.[78] Disrupted circadian rhythms will have negative outcomes directly related to pain. For example, for night shift workers, pain scores increase for cold nociception, heat nociception, and electrical stimulation.[79,80] Circadian rhythm disruption does not lead to sudden death in animal models or humans but can have long-term or short-term adverse health effects.[81] The glucocorticoid cortisol peaks at 8 a.m. and may be associated with daytime pain patterns.[82]

Harnessing the power of time to intervene in human disease has been a promising direction since the 2017 Nobel Prize in Physiology or Medicine discovered the relationship between the biological clock and human biology. Studies of several existing disease models have shown the potential of using circadian rhythms as a therapeutic strategy, such as sepsis, malignancy, and ischemia-reperfusion injury.[83] However, there are few detailed reports on circadian changes in chronic neuropathic pain. Also, there may be opposed physiological effects between animal models and humans, for example, melatonin has a sleep-promoting effect in humans and an arousal-promoting effect in nocturnal animals.

Circadian Rhythm in Pain Response

Circadian rhythms in pain behavior were first identified in 1987 in a study involving hamsters. Similar phenomena were later observed in different strains of mice. Subsequent research on various strains of mice revealed a more complex phenomenon: mice in C57BL/6 were found to have lower pain sensitivity in dark environments, while Swiss Webster mice had higher pain domains during the day.[84]

A significant circadian rhythm oscillation was found in almost all clinical conditions related to pain; for example, neuropathic and temporomandibular joint pain became intolerable around 8 p.m., while patients with trigeminal neuralgia and fibromyalgia experienced a marked increase in pain in the morning.[85] Individuals with acute pain also exhibit the circadian cycle of pain. Patients with biliary colic experience more severe pain at night, and after major surgery, the pain is more noticeable in the morning.[86] Different diseases realize different circadian rhythms.[87] Variations in pain disorders' circadian cycles are partly due to variations in these disorders' biology.[88] In a survey of patients suffering from diabetic

Table 1 Several Treatments for Diabetic Neuropathic Pain

Class	Drugs	Biological Target \Mechanisms	Region where Approved	Effects
Regulators approve treatment for painful diabetic neuropathy	Gabapentin	The α2δ subunit of calcium voltage-gated chan	United Kingdom and Australia	Pain relief in painful DPN and postherpetic neuralgia
	Pregabalin	The α2δ subunit of calcium voltage-gated chan	USA, Europe and Canada	Pain relief in painful DPN, spinal cord and postherpetic neuralgia
	Duloxetine	Inhibition of reuptake of serotonin and norepinephrine	USA, Europe and Korea, etc.	Pain relief in painful DPN, fibromyalgia and chronic musculoskeletal pain
	Capsaicin 8% patch	Removal of substance P from vanilloid nerve receptors	USA, etc.	Relief of neuropathic pain associated with postherpetic neuralgia and DPN
Not approved by regulators but used to treat neuropathic pain in diabetes	Venlafaxine	Inhibition of reuptake of serotonin and norepinephrine	USA, Europe, etc.	Pain relief in painful DPN
	Amitriptyline	Inhibition of reuptake of noradrenaline and serotonin in presynaptic neurons and antagonizing N-methyl-D-aspartate receptors	USA, Europe, etc.	Pain relief in painful DPN, neuropathic pain and fibromyalgia
	Thiotic acid	Antioxidant	USA, parts of Europe, etc.	Pain relief in painful DPN
	Carbamazepine/ Oxcarbazepine	Sodium channel blocker	USA, Europe, etc.	Pain relief in neuropathic pain
Treatments not yet agency approved but with positive reports from Phase 2 or Phase 3 trial	Mirogabalin[57,58]	The α2δ subunit of calcium voltage-gated chan		Pain relief in painful DPN and postherpetic neuralgia
	YJ001 spray[59]	Localized medicine		Pain relief in painful DPN
Treatments in clinical development	Palmitoylethanolamide (PEA)[60]	N-arachidonoylethanolamine and the ENCB system		Pain relief in neuropathic pain
	Platelet-rich plasma (PRP)[61]	Revascularization and regeneration		Pain relief in neuropathic pain
	Lidocaine medicated plaster (LMP)[62]	Topical treatment		Pain relief in painful DPN
Treatments showing pre-clinical efficacy	Naringenin[63]	Modulation of oxidative-nitrosative stress, cytokines and MMP-9 levels		Relief of pain in DNP rats
	Reboxetine[64]	Catecholaminergic and opioidergic system		Relief of pain in DNP rats

(*Continued*)

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Table 1 (Continued).

Class	Drugs	Biological Target \Mechanisms	Region where Approved	Effects
	Withametelin (WMT)[65]	MAPK/NF-κB signaling		Relief of pain in DNP rats
	Quercetin[66]	Rapamycin (mTOR) and p70 ribosomal S6 kinase (p70S6K)		Pain relief in DNP mice
	Nanocarriers: amitriptyline- and liraglutide-loaded proniosomes[67]	Control of inflammation and oxidative stress		Relief of pain in DNP rats
	Ajugarin-I[68]	TRPV1/TRPM8 nociceptors		Relief of pain in DNP rats
Non-pharmaceutical treatments in current use	Neurostimulation Transcutaneous electrical nerve stimulation (TENS)[69]			Pain relief in neuropathic pain
	Spinal cord stimulation (SCS)[70]			Pain relief in neuropathic pain

neuropathic pain, it was found that more than half of the patients had increased pain at night, and about 30% had consistent levels of pain during the day and night.[89]

Notably, pain itself can have an impact on circadian rhythms. Fibromyalgia and cancer-induced pain can disrupt the patient's circadian rhythm.[90] Breaking of molecular rhythms has also been observed in preclinical studies in selected sciatic nerve ligation models and spinal cord injury models.[91] However, the extent of this link between the effects of pain itself on circadian rhythms still needs to be further evaluated.

Although inflammatory and neuropathic pain has traditionally been distinguished from one another, some new research has revealed that this differentiation may not be as strong or even unanimous.[92] Fortunately, the diametrically opposite pain patterns seen in the circadian cycles of neuropathic and inflammatory pain will also serve as a basis for the difference in pain.

Animal Model and Circadian Rhythm of Neuropathic Pain

Modified nociceptive sensitivity is a key factor in identifying the existence of neuropathic pain in animal models.[23] Research has demonstrated that both diabetic peripheral neuropathy and postherpetic neuralgia exhibit a unique circadian cycle, with pain increasing at night and decreasing during the day.[93,94]

Analysis of nociceptive sensitivity in experimental animals is the first step in determining treatment by performing analyses of mechanical sensitivity or thermal sensitivity, but these experiments rarely consider circadian rhythms. Researchers separated each day into four time periods and examined the rats' pain thresholds in each period independently in a study on neuropathic pain in rats with CCI.[95] The study discovered that the rats' pain thresholds were higher when they were active than when they were at rest. At the same time, the rats were administered analgesics at various times, and it was discovered that analgesia administered during the active period was superior to that administered during the resting period.[95] N-methyl-d-aspartate receptor 2B (NR2B)-cAMP response element-binding protein (CREB)The CREB-regulated transcriptional coactivator 1 (CRTC1) signaling pathway can affect circadian rhythms in SCN.[96] After interferential injection of CCI mice with CREB/CRTC1 adenovirus to inhibit the expression of CREB and CRTC1 at 2-time points during the circadian period, ZT0 (from active to resting) and ZT12 (from resting to active), the aberrant pain behaviors of the mice were significantly reduced, and when the drug was administered at ZT0, the mice showed lower nociceptive sensitivity and the drug effect lasted for a longer period. While when administered at ZT12, the analgesic effect was less pronounced.[95] In the CCI model, a hormone associated with circadian rhythms, glucocorticoids, was also observed to induce the release of ATP from spinal astrocytes, producing a mechanically abnormal pain circadian rhythm.[97] In another study, nociceptive sensitivity was higher in rats during the inactive phase of paclitaxel-induced peripheral neuropathy (CIPN), and nocturnal (active phase) administration was superior to daytime (inactive phase) administration in terms of both analgesic effect and resistance. Significant circadian oscillations in the core clock protein BMAL1 were identified in satellite cells and spinal cord dorsal horn neurons.[98] Altered circadian rhythms of melatonin receptors and opioid receptors were observed in the SNI mouse model.[99]

The Mechanism of Circadian Rhythm of Neuropathic Pain

Changes in circadian rhythm are associated with neuropathic pain for a multitude of reasons. There is growing evidence that clock gene-driven rhythmic expression of various proteins is involved in injury perception and pain signaling. Alterations in relevant molecules in the clock gene feedback loop affect nociceptive sensitization in mice with disrupted circadian rhythms.[15] Studies have shown that during neuropathic pain, there are diurnal fluctuations in inflammatory modulators, and ion channels like calcium channels, naloxone receptors, and opioid receptors at different times of the day.[100–103] Meanwhile, the circadian rhythm of endogenous opioids is thought to be closely related to neuropathic pain, with beta-endorphin levels being lowest at night and highest in the morning.[104] Circadian fluctuations in mood can also affect the experience of pain.[105]

An adenovirus-mediated signaling pathway was also found to have a palliative effect on CCI-induced neuropathic pain in a model study on sciatic nerve injury. Neuropathic pain in rats was also found to be associated with diurnal variations in ATP release from astrocytes and glucocorticoid secretion.[95,97] It has been noted that in rodents, peripheral nerve damage affects the SCN, which disrupts the circadian rhythm of melatonin receptors in the hypothalamus.[99]

The immune system is also implicated with regard to circadian rhythms in neuropathic pain. Following the start of NP, there is a noticeable rise in T-cells, neutrophils, astrocytes, microglia, and other brain cells that have been shown to have circadian cycles that are also highly correlated with pain.[106,107] Circadian rhythms also exist for many cytokines and chemokines, which can act directly or indirectly on the spinal cord or sensory neurons to influence the perception of pain.[102]

Numerous scientific studies have established a robust connection between neuropathic pain and a few key circadian genes. The Tac1 gene, which encodes substance P, is involved in pain signaling. It has been demonstrated that CLOCK: BMAL1 drives circadian transcription of this gene in the dorsal root ganglia, indicating a direct biological mechanism between the circadian oscillator and neuropathic pain.[108] In a mouse model of CCI, the Per gene was also shown to exhibit circadian oscillations. Neuropathic pain brought on by sciatic nerve injury was alleviated by injectable medication targeting the Per1 gene (See Figure 2).[109]

Associated circadian rhythmic alterations in ion channels, and sensory receptors consistent with pain, are seen in both DNP and postherpetic neuralgia.

Circadian Rhythm of Microglia

Microglia are immune cells that are special to the nervous system and are engaged in the growth and development of the central nervous system as well as the process of mending damaged nerves.[110] Numerous cells, including astrocytes and immune cells, have been implicated in the research of diabetic neuropathic pain, with microglia being crucial in the genesis of pain.[111] Numerous animal models of neuropathic pain, including the CCI model, the SNI model, and the STZ-induced diabetes model, have shown activation of microglia.[112–114] 42 days following a successful induction, significant activation of microglia was shown in an animal model of STZ-induced diabetic neuropathic pain in rats. Remarkably, no activation of astrocytes was observed in the rats.[115] In STZ-induced DNP rats, alterations in the morphology of microglia may be seen, including changes in the thickness and retraction of protrusions as well as modifications to the hypertrophic morphology.[116] Spinal dorsal root neurons in DNP exhibit activation of the microglial signal-regulating proteins SFK and

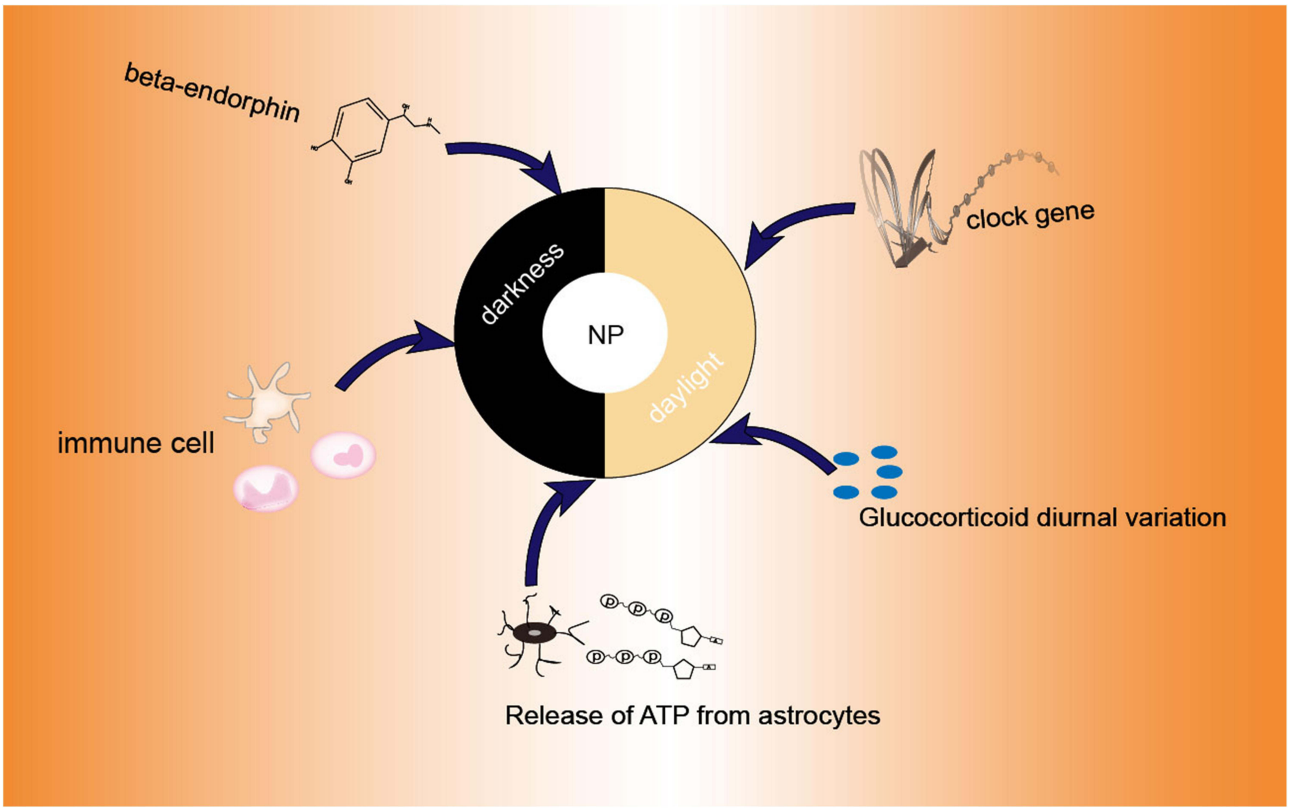

Figure 2 Causes of circadian rhythms in neuropathic pain.

EPK.[116] Phosphorylation of MAPK, involved in intracellular signaling such as JNK, p38-MAPK, and ERK, happens during microglia activation and has been linked to the development of neuropathic pain.[117,118] Phosphatase-induced MAPK inactivation reduces inflammation and eases diabetic neuropathic pain.[119] Tyrosine kinases (SFKs) play a role in the nervous system's development. DNP is formed when SFKs are phosphorylated, and DNP can be relieved by injecting SFK inhibitors intrathecally.[120,121]

The morphology of activated microglia differs from that of resting microglia. When microglia are activated, they undergo morphological changes to an amoeboid shape lacking branches and functional modifications related to gene expression. Resting microglia feature small branches and protrusions.[122–124] Two types of microglia activate M1 and M2. M1 microglia alter synaptic communication between neurons, which can result in neuropathic pain. In vitro experiments, interleukin 13 or interleukin 4 can induce the production of M2 phenotype microglia, which can produce pro-inflammatory and anti-inflammatory cytokines, respectively, and interferon-gamma or lipopolysaccharide can induce the production of M1 phenotype microglia.[125,126] After being activated, microglia release IL-10, which encourages polarization of the cell toward the M2 type, and IL-1β, and IL-6, which encourages polarization of the cell toward the M1 type.[127] Different models of neuropathic pain have been reported to exhibit varied degrees of dysregulation of the microglial ratio between M1 and M2 types.[128] Numerous studies have demonstrated the enormously beneficial effects of returning M1 and M2 microglia to a normal state of proportionality in the treatment of neuropathic pain.[129]

Even while our understanding of immune cells' circadian rhythms has improved recently, microglia have received less attention. The central and peripheral nervous systems include a high number of microglia, which are stimulated by lipopolysaccharides to release a large amount of cytokines.[130] Interestingly, cytokine expression in microglia after lipopolysaccharide stimulation differed at different times of the day. There was a significant circadian difference in the expression of pro-inflammatory cytokines TNFα, IL6, IL1β, and IL1R1 in microglia.[131]

Interestingly, microglia produced fewer inflammatory factors during the active phase (dark phase) than during the resting phase (day phase) in rats, but exposure to a small amount of light during the active phase increased the secretion of inflammatory factors by microglia.[131] As in Figure 2. Microglia were discovered to be more sensitive to immunological stimuli during the resting phase and the expression of their biological clock genes was altered in the absence of glucocorticoids in the animal model.[131,132] Some genes have been identified to exhibit rhythmic expression in central nervous system molecular studies in rat hippocampus microglia, and these genes exhibit a considerable drop in expression at the start of or during times of activity.[131] Microglia's clock genes have been observed to be less expressed in the cerebral cortex during resting periods, although the timing of the expression of cytokines produced by microglia, such as TNF-a and IL-6, varies.[132] Disruption of circadian rhythms exacerbated macrophage responses to LPS stimulation in vitro, and peripheral LPS injections enhanced the induction of TNFa and IL6 mRNA in microglia from mice exposed to dim light compared with darkness.[133]

Melatonin is regulated by the SCN and its secretion has typical circadian rhythm differences.[134] Melatonin has been shown to reduce neuropathic pain. Melatonin can act on microglia to alter intracellular MAPK cascade responses.[135] Tissue protease S is strongly associated with diabetic neuropathic pain, which is expressed in microglia in the central nervous system and exhibits a circadian rhythm. It can modulate synaptic strength in cortical neurons.[132]

It is important to note that relatively little study has been done on female rodents in this field; the majority of studies have been on males.[136]

Clinical Experiment and Treatment of Neuropathic Pain Circadian Rhythm

Clinical studies have shown that the intensity of pain feelings varies during the day for several pain-causing illnesses, including multiple sclerosis, cancer, and diabetic peripheral neuropathy.[106,137] Changes in circadian rhythm in neuropathic pain have been examined in two clinical trials.[138,139] Patients with diabetic neuropathic pain (DNP) and postherpetic neuralgia (PHN) participated in both trials. Every day in the morning, midday, and evening, the patients' levels of pain were measured and recorded by the experimenters. A subset of patients receiving round-the-clock opioid treatment or opioid combinations were found to still have a circadian rhythm to their neuropathic pain, indicating that opioids may not be able to effectively improve the circadian rhythm of this pain. Patients with both disorders were observed to show a gradual increase in pain intensity from morning to evening. Pain intensity increased significantly

from 08: 00 a.m. to 16: 00 p.m. and then again from 16: 00 p.m. to 20: 00 p.m. The mean relative difference in pain intensity from 8: 00 a.m. to 20: 00 p.m. was higher in patients with DNP than in patients with PHN.[94] At the same time, women and patients with diabetic neuropathic pain have more intense nociception at night, suggesting that the circadian rhythm of pain is modulated by multiple factors. Some external factors such as ambient temperature, humidity, tactile stimuli, etc., and internal factors include circadian fluctuations in endocrine regulation and physical activity.

Chronotherapy has been shown to be useful in the clinic. It involves treating a patient at specified times according to the circadian rhythms present in biology or in a particular ailment, regardless of the patient's or the treating physician's convenience. For instance, glucocorticoid inhibitors used at night can more effectively alleviate pain and other rheumatoid arthritis symptoms than those taken in the morning.[140] There is a circadian rhythm to the expression of opioid receptors, and research in rodents has shown that giving opioids at night produces superior analgesia and a faster recovery of nociception than doing so during the day.[141] Also, opioids can directly affect the circadian system, and a disrupted circadian rhythm can alter the efficacy of opioids. This effect usually leads to an increase in opioid use.[142]

Exosomes can significantly improve diabetes-induced peripheral neuropathy. In a rat model of DNP, exosomes alleviated neurovascular dysfunction, accelerated nerve conduction velocity, and increased pain threshold.[143] Exosomes are paracellular, 50–150 nm in diameter, and contain lipids, proteins, RNA, and other substances.[144] Through the transfer of genetic material, exosomes play an important role in intercellular communication. Exosomes derived from M2 macrophages can convert the vast majority of M1 macrophages in the body into M2 macrophages.[145] Microglia are a type of macrophage, and treatment of neuropathic pain with exosomes can convert activated microglia in vivo to the M2 phenotype. Microglia have their own circadian rhythms, and exosomes given at different times may affect microglia differently, which in turn may alleviate the increased pain at night in patients with diabetic neuropathic pain.

A 24-hour circadian rhythm exists for the a2d-1 subunit of the voltage-gated calcium channel, and a blocker of this subunit, gabapentin, administered at the correct time point enhances pain relief in mice.[146] According to a study, the most plausible explanation for the superior analgesic effect of oral probenecid in STZ-induced DNP rats during the active phase is a diurnal rhythm in the expression of the intestinal organic cation transporter Octn1.[147]

Gender Differences in Circadian Rhythm System and Neuropathic Pain

Investigations into circadian rhythms have revealed some intriguing phenomena. Men's circadian cycles are longer than women's, indicating that men and women have different biological clocks.[148] In a similar vein, research on neuropathic pain has revealed that women's nociception varies more throughout the day than at night and that female DNP patients have higher nociceptive sensitivity.[93] Women seem to be more susceptible to altered pain sensitivity with a lower pain field in most illnesses that produce neuropathic pain.[149] Gender is not often taken into account in clinical investigations, and male rats are typically chosen and female rats are rarely used as research subjects in animal models of pain.[150] It has been demonstrated that male and female mice have distinct nociceptive pathways in response to neuropathic pain caused by nerve injury. Microglia activation was linked to increased nociceptive sensitivity in male mice, but immunological T cells in the spinal cord facilitated nociceptive sensitization in female mice, independent of microglia.[151,152] According to a study, a long-chain non-coding RNA that prevents the release of pro-inflammatory cytokines has a neuropathic pain-relieving effect on female rodents.[153] LPS injections enhance nociceptive sensitivity in female patients in a way that does not occur in male patients, suggesting that neuropathic pain in female patients is more closely linked to the activation of peripheral immune cells.[154] Numerous studies have been conducted on the mechanisms underlying neuropathic pain, and the majority of these causative factors are found in men. Approximately 80% of these mechanisms do not apply to female patients, which presents a significant challenge to the clinical treatment of pain in female patients.[155] Male rodents have better efficacy than females in the treatment of pain with opioids, but in studies of humans, female patients have been more sensitive to the analgesic effects of opioids, which is consistent with the more pronounced rhythmicity of daytime pain in females.[156,157] Estrogen is associated with the circadian function of reactive astrocytes, and it is unclear whether sex differences in pain are associated with different gender characteristics and estrogen cycles.[158] Thus, additional research should be conducted on both gender variations in circadian rhythms and neuropathic pain.

Discussion

Managing individuals with clinical diabetes presents substantial challenges due to pain resulting from diabetic peripheral neuropathy. This is in spite of the clinical finding that pain from diabetic peripheral neuropathy has a diurnal rhythm and the discovery that rats in the CCI and CIPN models demonstrate circadian rhythmicity of pain. Studies presenting circadian cycles in STZ-induced DNP mice are still scarce, nonetheless. Future research has a lot of potential when neuropathic pain and circadian rhythms are combined. Microglia have been discovered to be crucial in studies of both DNP and circadian rhythms, thus it will be important to look into whether regulating microglia activation in conjunction with therapies involving circadian timing can affect DNP. The intermediary between the two is the microglia; more "links" might be investigated in the future. The reason temporal therapy—a treatment not available for other conditions—is available for neuropathic pain is because it has a circadian rhythm. This could have unexpected implications for neuropathic pain therapy in the future. Exosomes derived from MSCs are a type of natural drug carrier, and a variety of constituents within them have the ability to control the activation of microglia and influence their transformation. MSCs have achieved rational therapeutic effects in the treatment of many diseases, and an increasing number of studies have found that MSCs can effectively inhibit the activation of microglia. Exosomes have been shown in numerous trials to alleviate neuropathic pain. Exosomes have been used in several clinical disorders and have shown some benefits as a result of ongoing research. In conjunction with chronotherapy, the impact of MSCs or exosomes on microglia may offer a novel approach to the treatment of DNP. There might be the best time to treat DNP if exosomes are given at different intervals. Simultaneously, the gender disparities in pain behavior would justify further research into the mechanisms and management of pain. Given that male and female patients experience pain differently according to their circadian rhythms, treating patients of various genders at different times with alternative drug administration schedules may yield better outcomes. There should be an effort to transfer animal models to people with circadian rhythm abnormalities because the majority of studies on neuropathic pain are now carried out in rats, whose rest and activity cycles are completely different from those of humans.

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The authors report no conflicts of interest in this work.

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