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REVIEW ARTICLE

Recent advances in nanoplatforms for the treatment of neuropathic pain

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STUDY DESIGN: Narrative review.
OBJECTIVES: The objective was to summarize the literature on nanoplatforms in spinal cord injury (SCI) and describe their effect in facilitating experiments for SCI. Currently, the primary clinical treatment for neuropathic pain (NP) is drug therapy, but these traditional drugs have many disadvantages, such as high dose, rapid clearance from the circulatory system, off-target side effects, and cytotoxicity. Moreover, the treatment for NP is complicated by the existence of blood–brain barrier. In recent years, nanomedicine has been receiving increased attention; this novel modality could help deliver drugs to treat NP via nanoplatforms, making it a promising alternative therapy. The use of nanoplatforms can enhance pharmaceutic effectiveness by either avoiding rapid clearance from the blood or ensuring adequate concentration in the lesion.
METHODS: A literature review was conducted, with a focus on nanoplatforms that have been described in the experimental studies of neuropathic pain.
RESULTS: We provide a brief description of the roles of liposomes, polymeric nanoparticles, metal nanoparticles, micelles, and dendrimers in the treatment of NP and discuss the prospective development of the nanoplatform system for NP.
CONCLUSION: The emergence of various nanoplatform drug delivery systems can provide an advantageous resource tool for real-time diagnosis and effective treatment of SCI-related NP.

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INTRODUCTION

Neuropathic pain (NP), results from a lesion or disease affecting the somatosensory component of the nervous system, with a prevalence rate as high as ~7–8% in the population, and is characterized by either positive (increased somatosensory function) or negative (decreased somatosensory function) sensory signs and symptoms, including burning sensation, induced pain, and abnormal temporal summation [1]. In addition, ~80% of patients with spinal cord injury (SCI) have NP, of which 40% was reported as intense NP, which is a common chronic pain condition that greatly reduces the overall quality of life [2]. SCI occurs usually because of local spine deformation caused by mechanical damage and direct compression and injury of nerve elements and blood vessels from fracture and displaced bone fragments or disc material. SCI includes at-and below-level SCI-based NP, while at-level pain may consist of both peripheral and central NP, below-level pain is a central NP condition [3]. SCI can incur hyperactivity of neurons and glial cell activation, increasing intracellular and extracellular glutamic acid neuropeptide adenosine triphosphate proinflammatory cytokines and concentration of reactive oxygen species (ROS). These factors lead to maladjustment in the injured spinal cord and damage synaptic circuits, thus increasing spinal dorsal horn pain, and permanently causing NP Notwithstanding various therapeutic regimens that have been developed for NP, the treatment outcome of patients with SCI-based NP remains poor, and such patients continue to be affected by sleep disturbances, anxiety, and depression caused by pain.

Current traditional pharmacological treatments for NP are anticonvulsants such as lamotrigine, pregabalin, gabapentin, tricyclic antidepressants, selective serotonin–norepinephrine reuptake inhibitors, lidocaine, capsaicin, tramadol, strong opioids (morphine and oxycodone), and botulinum toxin A [4]. These conventional analgesics have limited therapeutic efficacy and some of these analgesics, such as anticonvulsants, tricyclic antidepressants, and strong opioids could produce typical central side effects such as drowsiness and dizziness, resulting in potential fall risk. The use of lidocaine and capsaicin 8% patch has only short-term analgesic effects in patients with peripheral local NP, and owing to the distinctive features of the neurovascular system, most non-invasive routes of drug delivery cannot access the central nervous system (CNS) [5]. Furthermore, most of these medicines show poor solubility in water. Thus, it is necessary to explore novel effective alternative therapeutic options to overcome these problems and develop anti-NP targeted therapies [6].

With the advancement of nanotechnology and biochemistry, it is possible to establish a nanoplatform drug delivery system for NP treatment. Research has shown that drugs can be lysed, implanted, encapsulated, or attached to nanoparticles, serving

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as a nanoplatform drug delivery system [7]. Nanoparticles, which comprise natural or artificial polymers with dimensions ranging from 1 to 1000 nm, can target central inflammatory sites [8]. Furthermore, modification of nanoparticles by active targeted molecules also contributes to effective drug delivery, transport through the blood–brain barrier, elimination of undesired off-target effects, and improvement in therapeutic efficacy.

The recent development and advancement in nanoplatforms for drug delivery in NP treatment is introduced and described in Table 1. Diverse types of nanocarriers, including poly lactic-co-glycolic acid (PLGA) nanoparticles, liposome nanoparticles, metal nanoparticles, nanomicelles, nanocapsules, and dendrimers, are being studied and developed for the treatment of NP.

Therefore, in this review, we provide a brief description of the roles of liposomes, polymeric nanoparticles, metal nanoparticles, micelles, and dendrimers in the treatment of NP and discuss the prospective development of the nanoplatform system for NP, especially SCI-based NP in the future.

RESEARCH ADVANCES IN NANOPLATFORMS FOR THE TREATMENT OF NP

Polymer nanoparticles—poly (lactic-co-glycolic acid) (PLGA)

PLGA has attracted considerable attention because of its biodegradability and biocompatibility, controlled release of the drug, protection of the drug or gene from decomposition, and ability to modify the surface for diagnosis and treatment of diseases [9].

PLGA is the most widely used drug delivery system and is effective in infiltrating tissues owing to its nano size [10]. Therefore, PLGA has been a promising nanoplatform for the treatment of NP, owing to its advantages such as good biocompatibility, safety and controllable degradation rate, continuous intracellular drug release, low cost, and ease of production.

The long-term use of oxaliplatin can inhibit the expression of Thioredoxin Interacting Protein (TXNIP) in sciatic nerve cells, which regulate autophagy, resulting in NP [11]. TXNIP induces NP in microglia by producing an inflammatory response through the inflammatory body axis. Liu et al. manufactured a PLGA-metformin nanoemulsion using double emulsion solvent diffusion method, which is used as a carrier and metformin as a cargo to target TXNIP [12]. Additionally, the nanoparticle can induce significant upregulation of TXNIP and autophagy-related indicators, increase the threshold of thermal sensitivity and mechanical prickling, inhibit neuropathic sensitivity, and alleviate NP.

In recent years, gene therapy based on siRNA silencing has attracted attention owing to its therapeutic potential in multiple diseases, which can degrade mRNA molecules by forming RNA-induced silencing complexes to interfere with the expression of specific protein-coding genes [13]. However, these molecules cannot reach their CNS targets as they are unable to pass the blood–brain barrier and, as a result, can be completely eliminated. Thus, Shin et al. designed P38 siRNA-loaded PLGA nanoparticles using the typical double emulsion method (W/O/W) so that hydrophilic P38 siRNA could be effectively embedded in PLGA nanoparticles [14]. After the application of p38 siRNA-PLGA nanoplatforms in a solid lipid nanoparticles (SLN) mouse model, the expression of p38-related inflammatory genes such as TNF-a was modulated, resulting in the loss of p38 phosphorylation in microglia of the spinal dorsal horn, thereby inhibiting microglia activation and alleviating NP [15]. The siRNA-PLGA nanoplatform could cross the blood–brain barrier and enter the CNS, concentrate p38 siRNA in spinal cord microglia, and target microglia-specific genes, which play crucial roles in NP.

Another study showed that CX3CL1 and its receptor CX3CR1 can also play important roles as promising novel targets in the treatment of NP. Similarly, a drug delivery system that can effectively deliver CX3CR1 siRNA to spinal microglia cells is needed [16]. Noh et al. synthesized PLGA-coated CX3CR1 siRNA nanoparticles with the conventional double emulsion method (W/O/W) using ultrasound and injected them intrathecally into mice (Fig. 1). In the spinal dorsal horn, the microglial activation in CX3CR1 siRNA-PLGA nanoplatform-treated mice was significantly reduced, the proinflammatory mediators were significantly downregulated, and mechanical tenderness was significantly alleviated. These studies suggest that PLGA-encapsulated CX3CR1 siRNA nanoparticles can effectively alleviate SNL-induced NP in mouse models through reduction in the microglial activity and the expression of proinflammatory mediators [17].

PLGA nanoparticles have shown unique advantages in enhancing the targeting of various drugs to the CNS, especially microglia cells. It can be embedded by highly specific microglial markers and a variety of therapeutic agents, facilitating absolute targeted therapy without altering other critical processes. The limitations of PLGA nanoparticles are that its encapsulation efficiency and siRNA delivery capability are lower than those of recombinant viruses. Hering et al. used fish embryo toxicity test to test the toxicity of polymer nanomaterials, and found that PLGA still had some toxicity, although it was very low [18]. Moreover, Lagreca et al. found that many parameters affect the drug loading of PLGA; of these the PLGA terminal cap had a significant effect on the drug loading rate, the ester-capped had a higher encapsulation, while the acid end group had a lower drug packaging efficiency. Therefore, the requirements for manufacture are strict [19]. Nevertheless, PLGA can be a promising effective drug delivery nanoplatform in precise treatment of NP.

Lipid-based nanoparticles

Lipid-based NPs can be categorized as SLN, NLCS, and liposomes [20]. SLN is a colloidal nanoparticle delivery system consisting of a biodegradable solid lipid core and stabilizer. It is a relatively new class of submicron-sized (50–1000 nm) nanoparticles acting as a safe, nontoxic, biocompatible, and temperature-sensitive lipid nanocarrier. Additionally, SLN is physically stable, can protect drug stability in vivo, slowly releases the drug, and has great biological endurance. Lastly, it can serve as an alternative drug carrier with various advantages such as increased bioavailability, drug delivery capacity of lipophilic and hydrophilic drugs, low cost, and high feasibility for mass production [21].

In a preclinical study, Sharma et al. designed an SLN system with a small particle size of 50–80 nm which could target the crucial gene trpv1 in NP [22]. The TRPV1-targeting siRNA (TRPsiRNA) SLNs nanoplatform demonstrates protection against physiological and nuclease-mediated degradation of encapsulated biomolecules, controlling and prolonging the release of their cargo and effectively transfecting cells. TRPsiRNA-SLNs was found to significantly reduce acute heat pain, capsaicin-induced pain, and injurious behavior, confirming the effective downregulation of TRPV1 [23]. The trpsiRNA-SLN system can maintain the biological activity and high transfection rate of trpsiRNA, ensuring the release of the coated trpsiRNA in a biologically active state to trigger a highly effective physiological effect, effectively silencing TRPV1 and significantly reducing the intensity and duration of capsaicin-induced harmful behavior. Sharma et al. also found that TrpsiRNA-SLNs have better therapeutic effect than trpsiRNA alone, even though trpsiRNA has ten times the amount of siRNA used in TrpsiRNA-SLNs nanoplatform [22].

Like most other nanoplatforms, SLNs also possess some disadvantages. High-pressure homogenization is a common method to prepare SLNs, but the high temperatures achieved during the process accelerate the release rate of drug and lipid degradation; in addition, coexistence of colloidal structures such as gels, drug sediment, particle size instability, and kinetic phenomenon are all shortcomings of SLNs [24]. A new generation of NLC NPs lipids can be prepared by mixing solid

Table 1. Examples of preclinical studies about different nanoplatform in the treatment of neuropathic pain.

Nano Carrier	Cargo	Target	Mechanism	Strengths	References
PLGA					
Metformin-loaded	Metformin	TXNIP	Metformin inhibits autophagy flux of sciatic nerve through TXNIP	PLGA nanoparticles can improve the expression of TXNIP	Liu et al. [11]
p38 siRNA-loaded	p38 siRNA	The P38 gene in microglia	The p38 siRNA-encapsulated PLGA nanoparticles inhibited SNL-induced microglia activation and p38 target protein expression	The p38 siRNA-encapsulated PLGA nanoparticles inhibit microglia activation and p38 target protein expression	Shin et al. [13]
CX3CR1 siRNA nanoparticles-loaded	CX3CR1 siRNA	CX3CR1 in microglia	CX3CR1 siRNA inhibited microglia activation, downregulated proinflammatory mediators, and significantly reduced mechanical tenderness	PLGA-coated CX3CR1 siRNA nanoparticles effectively alleviated neuralgia by reducing the expression of proinflammatory mediators	Noh et al. [16]
Lipid-based nanoparticles					
SLNs					
TRP siRNA-SLNS	TRP-siRNA	TRPV1	TRP-siRNA-SLNs reduce pain by silencing TRPV1	The TRP-siRNA-SLN system can maintain the biological activity and efficient transfection of siRNA, and ensure the release of TRP-siRNA in the form of biological activity, effectively silencing TRPV1	Sharma et al. [22]
NLCs					
CMZ-NLC	Carbamazepine	Nerve cell	The surface of the CMZ-NLC nanoplatform is negatively charged, and the release of beeswax is in a two-phase mode, so that CMZ can be continuously released	CMZ-NLC improves the oral bioavailability and analgesic properties of CMZ, and can avoid the production of toxic metabolites	Elmowafy et al. [26]
Liposomes					
Capsaicin-loaded liposome	Capsaicin	Skin	The liposome nanoplatform improved the solubility of capsaicin, and the liposome coated capsaicin lost the chance to contact the gastric mucosa, avoiding the gastric mucosa stimulation response	Capsaicin-loaded liposome increased the relative bioavailability of free capsaicin by 3.34 times and significantly reduced the irritation of gastric mucosa	Zhu et al. [30]
Metal NPs					
7CZ-Ab NPs	Microglia-specific antibodies	Microglia	Cerium dioxide nanoplatform can promote the delivery of microglia-specific antibodies to microglia cells, thus eliminating proinflammatory cytokines and ROS in microglia cells, and inhibiting the activation of microglia cells quickly and effectively	The appropriate delivery strategy for cerium dioxide NPS allows it to be specifically delivered to target cells or tissues and contained only within the restricted area of disease	Choi et al. [37]
GNR complex	siRNA	TNF	GNR Complex nanoplatform selectively silenced the expression of TNF in the hippocampus, thus significantly reducing pain perception	GNR Complex, as a nanocarrier, provides the stability of siRNA and the controlled release of target sites	Gerard et al. [41]
Nano-Micelle					
Nano-micelle sPLA2 micelle platform	sPLA2 inhibitor—TEA-PC	sPLA2	The sPLA2 micelle platform can effectively release the sPLA2 inhibitor TEA-PCA according to the different activities and expressions of sPLA2, thereby reducing neuropathic pain by down-regulating spinal nerve immune inflammation	The SPA2 micelle platform targeted increased drug concentration in inflammatory tissues and also reduced toxicity and side effects in non-target tissues	Kartha et al. [45]

Table 1. continued

Nano Carrier	Cargo	Target	Mechanism	Strengths	References
SMA-WIN micelles	Cannabinoid	Cannabinoid receptor agonists	SMA-WIN micelles targets cannabinoids to inflammatory tissues in the nerves to produce a more effective and lasting analgesic effect	The high permeability and targeting of SMA-WIN can reduce inflammation and subsequent neuropathic pain	Linsell et al. [47]
Nanocapsules					
BMA-Cy5 nanocapsule	Aprepitant	NK1R	BMA-CY5 nanocapsules inhibit SP-induced neuronal activation in the spinal cord, thereby accurately suppressing the signaling events that cause neuropathic pain	BMA-Cy5 nanocapsule enhanced targeted drug delivery with more effective and long-lasting pharmacological effects than free aprepidine	Ramírez-García et al. [56]
Dendrimer NPs					
Morphine prodrugs complexed with PAMAM dendrimer	Morphine Prodrugs	Nerve cell	The structure of the complex between morphine prodrug and PAMAM dendritic macromolecule can slowly control morphine release, thus prolonging morphine analgesia and duration	The complexation with PAMAM dendrimer can increase the solubility of morphine prodrugs in vivo without changing the pharmacokinetics of morphine	Ward et al. [62]

PLGA poly lactic-co-glycolic acid, *TXNIP* thioredoxin interacting protein, *CX3CR1* a chemokine for neuron-to-microglia signal transduction, *TRP* siRNA-SLNS, TRPV1-targeting siRNA (TRPsiRNA) SLNs nanoplatform, *TRPV1* transient receptor potential vanilloid 1, *CMZ-NLC* carbamazepine nano-lipid carrier nanopartical, *7CZ-c* ceria-zirconia nanoparticles with anti-mouse/human CD11b antibodies, *GNR* gold nanorods, *TNF* tumor necrosis factor, *sPLA2* secretory phospholipase A2, *TEA-PCA* thioetheramide-PC, *SMA-WIN* nanoplatform based on styrene maleic acid (SMA) and the potent CB1/CB2 receptor agonist cannabinoid WIN 55,212-2 (WIN), *BMA-Cy5* nanoplatform formed by nanocapsule with the hydrophobic NK1R antagonist aprepitant (MK-869) to synthesize diblock copolymers with the same hydrophilic shell, *PAMAM* polyamidoamine.

lipids with liquid lipids of various shapes. The adjunction of liquid and solid lipids destroys the conventional lattice structure, increases the proportional structure of nanoparticle irregular crystal forms (which are essential for enhancing the spatial capability of nanoparticles), and improves the drug delivery ability; liquid lipids are enclosed within the ambient solid lipid barrier. This particular structure allows NLCs to maintain a rigid framework at room temperature, thus controlling drug release in vivo [25].

Carbamazepine (CMZ) is another effective drug for treatment of NP in murine models, while poor bioavailability, continuous dose adjustment, and toxic effects of long-term use are major barriers to CMZ use [26]. To eliminate these obstacles, Elmowafy et al. successfully manufactured an NLC based on stearic acid and beeswax using a high shear homogenization/ultrasound technique. They integrated it with CMZ, which has a nanometer size range; this resulted in controlled-release ability and excellent physical stability [27]. CMZ-NLC improved the oral bioavailability and analgesic properties of CMZ, while reducing toxic metabolites and alleviating the adverse effects of CMZ.

Liposomes are spherical vesicles composed of one or more phospholipid layers that range in size from nanometers to microns; these have fully biodegradable properties and can encapsulate hydrophilic drugs in the inner aqueous phase and lipophilic drugs within the phospholipid bilayer to generate microcapsules of different sizes [28]. Liposomes have the advantages of fine particle synthesis, drug carriers, and improved therapeutic effect, which allows loading of some hydrophobic drugs. Compared with single drugs, liposome drug-loaded nanoplatforms release drugs slowly, reduce the toxicity of drugs to cells, and prolong the action time of drugs to show better drug activity [29].

Zhu et al. successfully developed a highly stable oral liposome containing capsaicin using cholesterol, sodium cholic acid, and isopropyl myristic acid as raw materials for the first time [30]. In gastric mucosa stimulation studies, liposome-encapsulated capsaicin has been shown to be safe for oral administration, significantly reducing gastric mucosal irritation, with increased relative bioavailability that is 3.34 times higher than that of free capsaicin. Consequently, liposome nanomaterials are expected to be used as a carrier system for hydrophobic drugs, improve the oral bioavailability of capsaicin, and become a new choice for NP treatment.

Recent studies highlighted that the clinical application of novel cannabinoid receptor agonist CB13, an excellent drug for NP treatment, is severely restricted by the influence of systemic metabolism, lymphatic transport, enterohepatic recirculation, and specific lipoprotein binding [31]. Thus, the use of novel carrier systems becomes an attractive strategy for the development of such compounds as a valuable therapeutic approach for NP. Durán-Lobato et al. used liposome nanoparticles as a nanoplatform for cannabinoid delivery system; these combine the best features of other colloidal carriers and can be made from physiological lipids in a variety of ways [32].

Cannabinoid liposome nanoplatforms, as lipophilic compounds, can reduce the initial metabolism and lymphatic absorption of cannabinoids, improve the gastrointestinal absorption of cannabinoids, and increase the oral bioavailability of cannabinoids to enhance the effect of cannabinoids on NP. It demonstrated that the cannabinoid-loaded liposome nanoplatform has a potential clinical application for the treatment of NP [33].

However, there are still some limitations for the use of liposomes in the clinical treatment of NP. Despres et al. found that the surface charge of liposome nanomaterials could affect immune reactions [34]. Villegas et al. also reported that liposome nanomaterials were characterized by low stability and poor in vivo stability in the presence of serum proteins and could produce certain human toxicity [35].

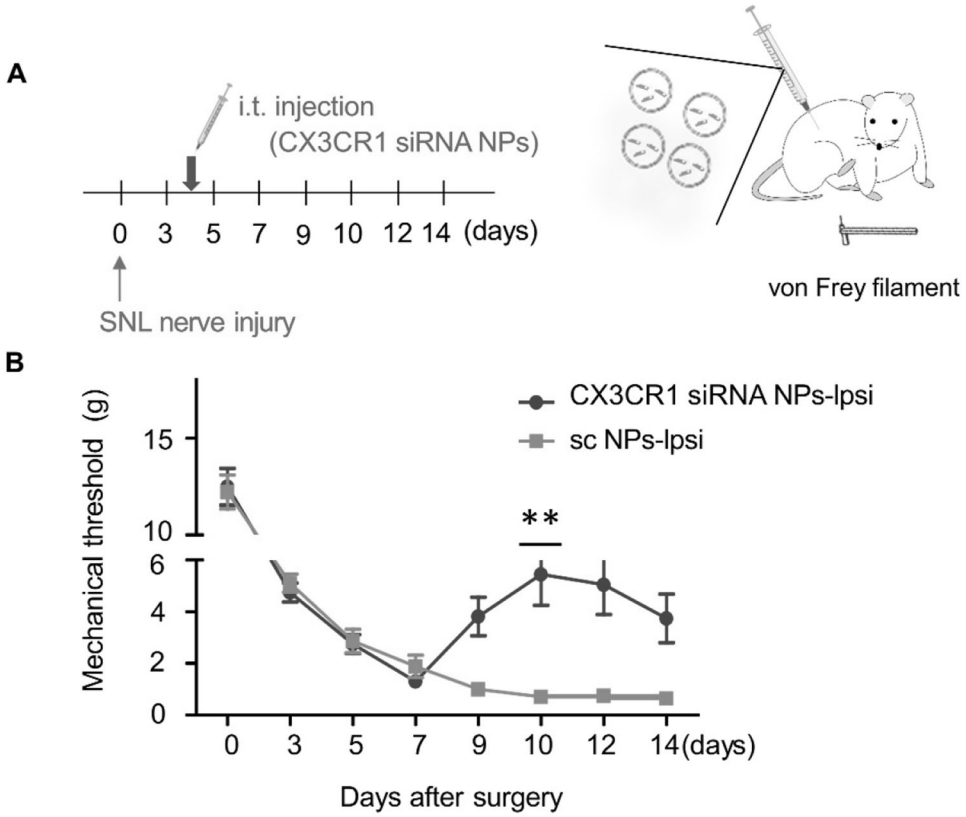

Fig. 1 Intrathecal injection of PLGA-encapsulated CX3CR1 siRNA nanoparticles alleviates the neuropathic pain induced by spinal cord ligation in rats. A Rat model of neuropathic pain was induced by spinal nerve ligation at the L5 vertebra. **B** PLGA-encapsulated CX3Cr1 siRNA nanoparticles increased the mechanical pain threshold in rats, SNL means spinal nerve ligation; Ipsi means ipsilateral. Data are presented as the mean ± SEM (*t*-test, one-way ANOVA, $^{**}p < 0.01$ versus VS siRNA NPs). Reproduced from Noh et al. [17] with permission from *International Journal of Molecular Sciences*.

Metal nanoparticles

Metal NPs are a promising delivery vector owing to their persistent existence in cells and ability to escape enzymatic degradation. They have a large body surface area, which can make the embellished metal nanoparticles carry drugs, thereby improving the solubility, and biological efficacy of the drugs, as well as having unique photonic properties [36]. In current studies, metal nanoparticles have been proved to have significant effects for NP in in vitro and in vivo experiments as they can enable antibodies or drugs to actively target disease sites, and can simultaneously play targeting, diagnostic, and therapeutic functions in the treatment process [35–41].

Neurological damage caused by abnormal ROS in the spinal cord leads to the activation of proinflammatory spinal microglia, which play a key role in subsequent pain sensitization [38]. Therefore, it is important to reduce the ROS level of microglia for preventing the occurrence of NP. In recent years, compared with natural antioxidants, nano-antioxidants have attracted extensive attention owing to their advantages such as easy mass production, high thermal and biological stabilities, multi-functionality, and adjustable performance [39]. Choi et al. used the oxidation of microglia-specific antibody parcel ceria nanoparticles (CZ nanoparticles) to treat NP. These can help microglia-specific antibodies to pass through any barrier so that targeted drug delivery can help reduce the release of inflammatory factors of microglia such as IL-1β、IL-6 and NO and ROS and allow it to quickly and efficiently suppress the activation of microglia (Fig. 2) [40]. At the same time of treatment, the appropriate delivery strategy of cerium dioxide nanoparticles allows it to be specifically delivered to target cells or tissues and is limited only to the central region of the disease. CZ nanoparticles inhibit the expression of pain-mediated genes in microglia and significantly reduce the mRNA expression levels of inflammatory mediator, thereby genetically reducing the occurrence of pain. CZ nanoparticles significantly improved mechanical tenderness in a spinal nerve transection-induced NP mouse model demonstrating its analgesic effect.

As previously stated, proinflammatory TNF is a key mediator in the pathogenesis of NP; thus, drugs or genetic manipulation that inhibit TNF can reduce hyperalgesia [41]. Small interfering RNAs can be used to block the expression of specific genes in the brain, but their effectiveness is short lived (1–3 days) and they need to be used in large quantities. Thus, a suitable vector is needed when using siRNA to treat NP [42]. Gerard et al. used inert gold nanorods (GNRs) as nanometer carrier which provides stability to siRNA and gumming point control release, and found that the TNF-siRNA nanometer platform can selectively inhibit the expression of TNF in the CA1 region of hippocampus. Selectively inhibiting the production of TNF can block the induction of related pain cytokines and enhance the release of monoamines, thereby disrupting the malignant NP cycle and significantly reducing the hyperalgesia and mechanical ectopic pain in NP [43].

Metal nanoparticles also have inevitable limitations. In animal experiments, silver nanoparticles were reported to cause some dose-dependent toxic reactions through the release of silver ions from the particle surface, such as changes in neurotransmitter levels, liver enzymes, heart expansion, and immune response [44] Similarly, Sharma and other researchers also observed in the experiment that the nanoparticles of silver and Cu nanoparticles could induce neurotoxicity in rats or mice after administration through systemic or intracerebral pathways, in which the glial axons and endothelial cells were most obviously damaged, thus

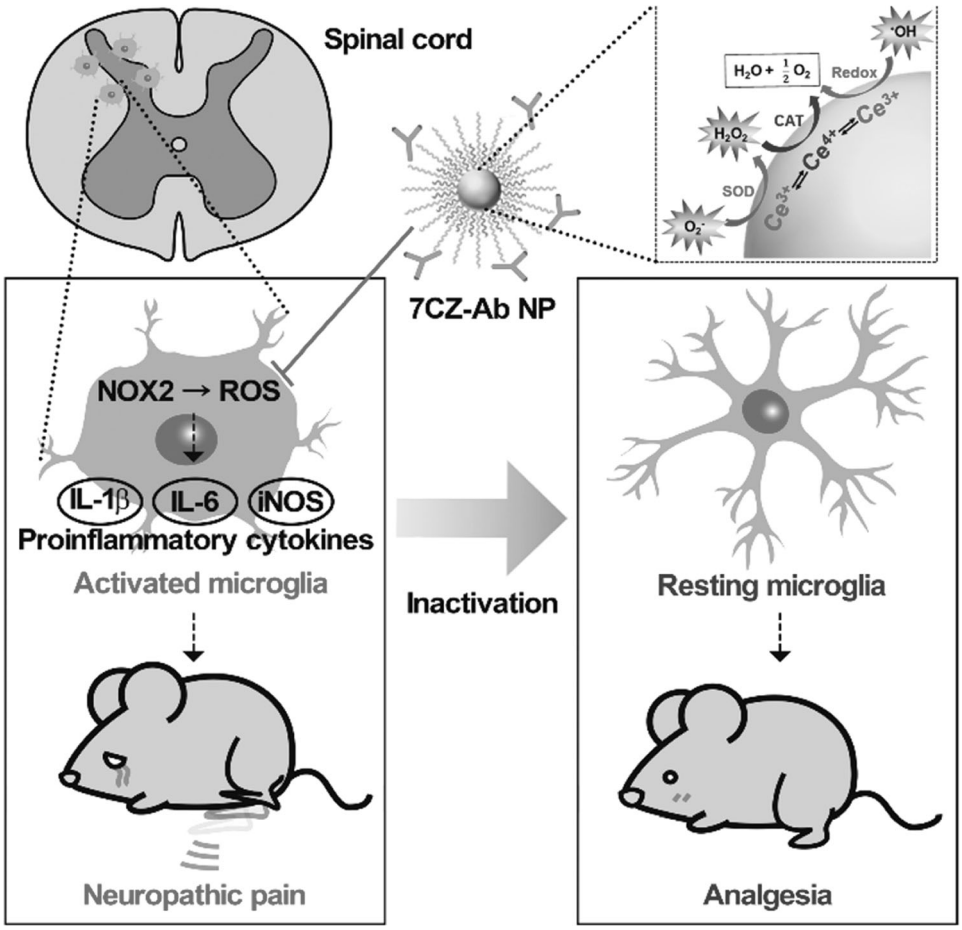

Fig. 2 7CZ-Ab NPs can rapidly inhibit the activation of microglia cells and downregulate the ROS and proinflammatory cytokines, thus it can quickly and effectively treat neuropathic pain in rats. Reproduced from Choi et al. [40] with permission from Nanoscale.

changing the sensorimotor and cognitive functions of experimental animals [45].

Micelles

Micelles are nanostructured material formed by self-aggregation of amphiphilic molecules in water above a certain critical micelle concentration; it is usually composed of a core-shell and amphiphilic block copolymer [46]. It is a unique and versatile material that can encapsulate hydrophobic drugs and can prolong their circulation in the blood by their hydrophilic shell; thus, it can be a very promising nanocarrier system with a fairly high capacity to carry drugs [47]. The micelle size ranges from 10 to 100 nm and has many unique properties such as stability, excellent biocompatibility in vivo, continuous circulation in the blood with high permeability to nerve inflammation tissues, and integration of a large number of hydrophobic drugs, which can contribute to drug targeting of NP and reduce nonspecific targeting of normal cells.

It was found that the phospholipase A2 (PLA2) family is one of the powerful inflammatory mediators involved in the immune regulation of spinal nerve pain. It recognizes and catalyzes the hydrolysis of the SN-2 ester bond of glycerides, releasing free fatty acids involved in tissue damage that leads to the development of NP [48]. Therefore, SPLA2 is a sensitive marker of spinal cord neuroinflammation and painful neurologic injury, and it can be used as a therapeutic target for NP. Kartha et al. prepared therapeutic nanoparticles based on phospholipid micelles by adding the SPLA2 inhibitor TEA-PC to hydrophobic superparamagnetic iron oxide nanoparticles, a nanoplatform capable of releasing a payload based on SPLA2 activity (Fig. 3) [49]. This delivery system increases the effective delivery concentration of the drug to the inflammatory target tissue and reduces the total dose required. Thus, it increases the effective concentration of the drug administered to the target tissue, thereby requiring less total dose, and reduces the toxic side effects on the surrounding nerve tissues and can release their loads according to the pathology of the pain itself.

Synthetic cannabinoids have previously been shown to alleviate hyperalgesia and tactile pain in rat models of NP, but its psychiatric side effects and low blood–brain barrier penetration severely restrict its clinical use [50]. Linsell et al. successfully synthesized the water-soluble nano-micellar platform SMA-WIN based on styrene maleic acid (SMA) and the potent CB1/CB2 receptor agonist cannabinoid WIN 55,212-2 (which is a chemical described as an aminoalkylindole derivative, which produces effects similar to those of cannabinoids such as tetrahydrocannabinol). It was loaded with water-soluble cannabinoids such as cannabinoid esters [51]. Highly loaded nano-micelle SMA-WIN can encapsulate hydrophobic molecules in hydrophilic structures so that a more stable structure can be formed between styrene groups and WIN. Further, it has ideal targeting delivery conditions and can selectively deliver cannabinoids to inflammatory tissues in NP. SMA-WIN can reduce the CNS' effects of embedded WIN by restricting its transport across the blood–brain barrier. The high permeability of SMA-WIN can directly target the site of neuroinflammation, reducing the inflammatory response and subsequent NP, and producing more effective and lasting analgesia.

The stability of polymer nanomicelles is closely related to the matrix material. Miller found that peG-PVPY micelles have lower

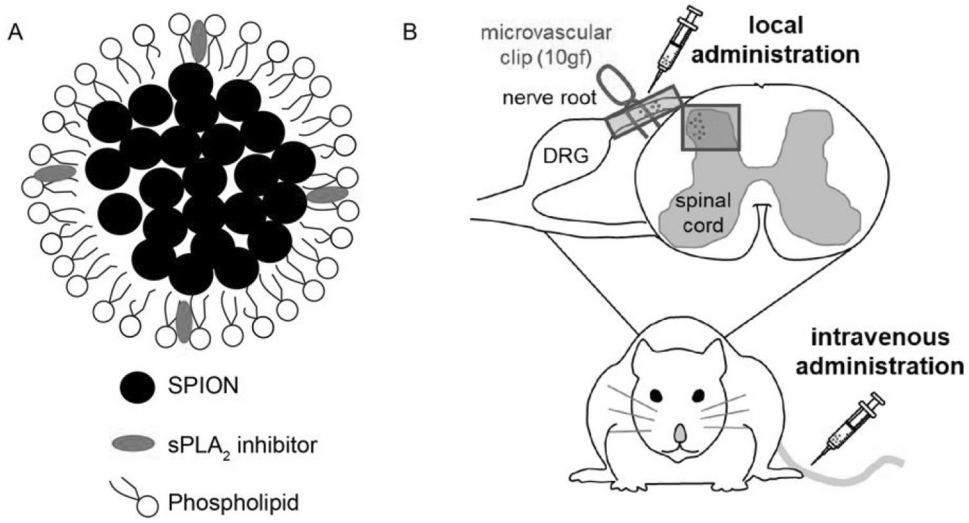

Fig. 3 Structure chart of nanomicelles structures loaded with sPLA2 inhibitors and their application in rat models of neuropathic pain. A The phospholipid and hydrophobic SPIO nanoparticles were assembled and then sPLA2 inhibitors were inserted into them to form sPLA2 Inhibitor-Loaded phosphoolipid Micelles. **B** sPLA2 inhibitor-loaded nanomicelles were used to treat neuropathic pain in a rat model. Reproduced from Kartha et al. [49] with permission from *ACS Nano*.

serum stability than polyester based micelles and peG-PVPY micelles rapidly become unstable after 3 h using a assay based on Foerster Resonance Energy Transfer [52]. In addition, Horn et al. found that nanomicelles may not be stabilized without certain temperature conditions and ionic strength [53]. The above reasons limit the utility of micelles to practical clinical applications.

Nanocapsules

Nanocapsules are nanoscale sac-like systems with a central cavity in which drugs can be encapsulated. Its central nucleus is encased in an envelope polymer membrane for surface binding of antibodies or targeted drugs [54]. In the past decade, nanocapsules have become the focus of research because of their protective coating functions, such as protection from spontaneous combustion, easy oxidation, and slow release of active ingredients [55]. Interfacial polymerization and nano-deposition are the best methods to prepare nanocapsules, and extremely high reproducibility makes nanocapsules a potential product candidate for biomedical applications, such as genetic engineering, radiation therapy, controlled drug delivery, and nanocapsules for anti-infection bandages [56].

Several studies indicate that neurokinin 1 receptor (NK1R) in the endosome is an important target for the relief of NP [57]. Endocytic inhibitors or antagonists targeting these receptors may provide an effective anti-NP effect. Thus, Ramirez-Garcia et al. assembled a nanocapsule with the hydrophobic NK1R antagonist aprepitant (MK-869) to synthesize diblock copolymers with the same hydrophilic shell to form pH-responsive BMA-Cy5 nanoparticles [58]. After being injected into the peritoneal cavity of rodents, BMA-Cy5 nanoparticles enter cells through dynamically dependent endocytosis, triggering drug release according to changes in endosomal and lysosomal pH values. This inhibits SP-induced neuronal activation in the spinal cord, accurately suppressing endosomal signaling events and leading to NP. Compared with aprepitant alone, the reactive BMA-CY5 nano-encapsulation platform can improve the stability and efficacy of the drug in the diseased tissue, tolerance, and transfer and retention; enhance the targeted drug delivery; and avoid side effect [59].

Organic selenium compound 2 (OMEPHSE2) is effective in reducing mechanical injurious behavior as well as PSNL-altered levels of inflammatory and apoptotic proteins (PSNL is a mouse model of NP that mimics some of the changes associated with the pathology of NP in humans). Therefore, OMEPHSE2, as a new synthetic molecule with pharmacological activity, has great potential in the treatment of NP. However, its properties such as poor water solubility of the organic selenium compounds may affect its overall bioavailability, thus affecting the biological effects. These limitations have delayed the progression to its usage in the clinical setting [60]. Henrique et al. recently found that compared with free OMEPHSE2, OMEPHSE2-nanocapsules extended their pharmacological activity, improved the biodistribution characteristics of OMEPHSE2 without any toxic effects, and enhanced pain resistance [61]. These can be attributed to its superior bioavailability and continuous controlled release of the drug.

Nanocapsule parameters such as capsule radius distribution, capsule surface, thickness, permeability of the capsule membrane, and its thermal or chemical decomposition determine whether it can be used to achieve effective controlled release and drug targeted therapy [62]. However, the excessively harsh preparation process and preservation condition limits its clinical application in the current NP therapy.

Dendrimers

Dendrimers are nano-sized and three-dimensional globular polymeric structures. Drug molecules can be attached on the functional groups on the surface or inside the dendritic macromolecules [63]. Dendrimers are viewed as excellent drug delivery nanoplatforms owing to their size monodispersity, high drug payloads, diverse surface functionalization capability, molecular stability, degradability, and the ability to transport hydrophobic and hydrophilic drug molecules [64]. Additionally, the size, shape, and composition of dendrimers can be accurately controlled. Owing to its slow-release properties, drug-bound dendritic macromolecular nanoplatforms have lower cytotoxic effects than free drugs, and the combined drug therapy has a strong synergistic effect.

It is generally acknowledged that oral morphine sustained-release formulations require continuous administration and complex dosing mechanisms, thus limiting their clinical use [65]. The multifunctional dendrimers are ideal “carriers” for hydrophobic drug encapsulation or complexation, which is particularly attractive in clinical therapeutic applications. Brent et al. developed morphine prodrugs complexed with PAMAM dendrimer by combining esterase-activated morphine prodrugs with surface-modified fifth generation

(G5) PAMAM dendrimers [66]. Complexation with dendritic macromolecular nanopolymers allows the solubility to increase and slow controlled release of morphine proagents in vivo without altering the pharmacokinetics of morphine, thereby enhancing and prolonging the analgesic action and duration of morphine in animal neuropain models.

However, transfection efficiency of dendrimers depends on high charge density. Nevertheless, increased charge density leads to cell membrane destruction, which leads to cytotoxicity [67], and they can be quickly cleared by the reticuloendothelial system in vivo circulation, which reduces their therapeutic effectiveness in the NP model [68].

CONCLUSION

We summarized various nanoplatforms for the treatment of NP that play a crucial role in solving conundrums in the current single-drug treatment for NP, especially SCI-related NP. These can deliver drugs to the CNS target more efficiently and reduce the accumulation of drugs in non-target nerve tissues, thus reducing various toxic side effects. However, there remain some concerns that must be addressed to better utilize nanoplatforms for NP, such as nanoparticle instability, insufficient drug circulation time in the body, lower blood–brain barrier crossing rate, and neurotoxicity. Furthermore, silver nanoparticles can reduce the value of transendothelial resistance, resulting in the destruction of the blood–brain barrier [69], while polymeric PLGA have drawbacks such as poor drug loading and potential chronic-systemic toxicities. Lipid-based nanoparticles face similar limitations as those of PLGA including insufficient biodistribution, the risk of stimulating an immune response, and potential toxicity. Metal NPs with surface modifications easily cross the blood–brain barrier. Thus, these tend to accumulate in the brain, especially in the cortex and hippocampus, resulting in reduced glutamate uptake by astrocytes; subsequently, this leads to a potentially damaging effect on brain function and an increased risk of neurodegenerative processes. The use of micelles is limited by its low stability, short shelf life, and interbranch reproducibility. Nanocapsules overcome the drawbacks of lipid-based nanoparticles such as low loading capacity of lipophilic drugs and unstable characteristics. However, nanocapsules have a complex manufacturing process and low mechanical system stability. Dendrimers have some disadvantages such as rapid clearance by the reticuloendothelial system, toxicity due to the interaction of the amine terminated group with the cell membrane, low transfection efficiency, and lack of controlled-release behavior, which reduce their therapeutic efficiency [70].

Variations in the size of nanoplatforms may affect their physiological stability; thus, careful consideration of the nanoparticle design, mass production capacity, and standardized characterization are necessary to ensure complete conversion of nanomaterials into clinical products for the treatment of NP. Furthermore, toxicity, degradation products, metabolic pathways, and system performance evaluation of nano-drug delivery platforms in vivo need to be studied further. Designing the right clinical trials is critical to ensure the use of nanoplatforms in clinical settings; individual, personalized, and patient-centered nanoplatform drug delivery system selection should be followed, and nanoparticles alone, which is the foundation of nanoplatforms, should be established as a control group to demonstrate its impact in clinical trials. In conclusion, the nanoplatform drug delivery system is a promising prospective clinical application for patients with NP, especially SCI-based NP. We hope that therapeutic strategies combined with nanoplatforms will not only provide a better diagnosis and effective treatment for NP in patients with SCI, but that they will also help provide a novel research focus on pain.

DATA AVAILABILITY

Previously reported data were used to support this study and are available at DOI. These prior studies (and datasets) are cited at relevant places within the text as references.

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AUTHOR CONTRIBUTIONS

BY was responsible for conducting the search and writing the report; KW was responsible for interpreting results and text checking; XX was responsible for screening potentially eligible studies; JJ and YL contributed to experimental design and provided feedback on the article.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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