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Review Paper

Histopathological Effects of the Intrathecal Chondroitinase ABC Administration in Spinal Cord Injured Rats: A Systematic Review

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ABSTRACT

Introduction: Chondroitinase ABC (ChABC) has been considered a potential treatment for spinal cord injury (SCI). We aim to identify and evaluate the histopathological effects of intrathecal ChABC administration in SCI rat models.

Methods: We searched PubMed/MEDLINE, Scopus, Web of Science, Embase, and Cochrane Library for studies published from the inception of each database until November 22, 2022.

Results: Of 3857 screened citations, 17 studies met eligibility criteria and were entered into the qualitative analysis. Sixteen studies were of high quality, and one study was of medium quality. The four main rat strains used in studies were Sprague-Dawley, Wistar, Lister hooded, and Long-Evans. ChABC treatment phases were considered acute (within 24 hours after injury), subacute (5 or 7 days after injury), or chronic (4 or 6 weeks after injury). Accordingly, ChABC administration in the acute phase of injury significantly reduced cyst formation and promoted

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tissue preservation and sensory neuron plasticity. Regardless of the treatment phase, ChABC administration significantly promoted serotonergic and corticospinal fiber plasticity. Nine of the 14 studies reporting on functional outcomes found that ChABC administration, alone or in combination with other treatments, including rehabilitation, improved motor function.

Conclusion: The specification of anatomical changes associated with ChABC treatment can explain the functional improvements reported with its use in SCI. The limited studies on more clinically relevant contusion and compression injury models warrant further investigation of these models and alternative treatment phases.

Highlights

- The current study evaluates the histological effects of Chondroitinase ABC (ChABC) injection into the spinal cord in rat models of spinal cord injury (SCI).
- Acute-phase administration of ChABC significantly reduced cyst formation and enhanced tissue preservation.
- It also promoted plasticity and regeneration of sensory neurons.
- Across all phases, ChABC enhanced serotonergic and corticospinal fiber sprouting, suggesting broad regenerative effects.
- The anatomical changes induced by ChABC have important implications for SCI treatment strategies.

Plain Language Summary

When the spinal cord is injured, it can cause serious problems with movement and feeling. Scientists are searching for ways to help the body repair itself after such injuries. This study looked at many earlier experiments that used a special substance called ChABC, which helps clean and fix the damaged part of the spine. The researchers reviewed the results of 17 studies on animals. They discovered that when ChABC was given soon after the injury, it stopped large scars from forming and helped protect the healthy parts of the spinal cord. It also allowed new nerves to grow and reconnect, making it easier for the body to heal and work better again. These positive effects were seen whether the treatment was given early or later after the injury. Overall, using ChABC helped the spinal cord recover better and improved nerve repair in animals. Scientists believe that it could one day help people with spinal injuries, but more research is still needed to make sure it is safe and effective for humans.

Introduction

Traumatic spinal cord injury (SCI) is a frequent condition that significantly burdens societies (Ackery et al., 2004; Ahuja et al., 2017; Singh et al., 2014). SCI patients have numerous therapeutic challenges since neurologic recovery is limited despite rehabilitation.

There is a growing body of data and knowledge regarding SCI mechanisms and the resulting histopathologic effects. The secondary injury after SCI begins with the migration of inflammatory cells and marked inflammation at the injury site, resulting in cell toxicity and neuronal damage (Donnelly & Popovich, 2008; Hausmann, 2003). Myelin is one of the key inhibitory factors following SCI. Unlike Schwann cells in the peripheral nervous system, spinal cord oligodendrocytes do not clear injured axons or myelin debris following SCI. Also, oligodendrocytes do not recruit macrophages or microglia to assist in this process (Lemons et al., 1999).

In the subacute phase of secondary injury following SCI, astrocytes become reactive and produce intermediate filaments through a process called astrogliosis, leading to the formation of a glial or perilesional scar around the injury site. This perilesional scar has tremendous effects in restoring the blood-brain barrier, supporting wound contraction, minimizing leukocyte infiltra-

tion, and limiting neuronal damage and demyelination (Faulkner et al., 2004). However, it inhibits later neuronal plasticity, axonal regeneration, and sprouting (Fitch & Silver, 1997; Herrmann et al., 2008; Karimi-Abdolrezaee & Billakanti, 2012). Expression of chondroitin sulfate proteoglycans (CSPG) is one of the major parts of glial scar formation (Jones et al., 2002; Morgenstern et al., 2002). Thus, glial scar removal or clearance by targeting CSPGs in the perilesional scar may create an environment conducive to spinal cord regeneration.

Chondroitinase ABC (ChABC), a bacterial endolyase, removes glycosaminoglycan chains from CSPG, which causes CSPG proteolysis after its formation (Fawcett, 2015; Wang et al., 2008). ChABC-targeted proteolysis is safer than enzyme therapy, which has been used previously (Guth et al., 1980). Enzyme therapies (including trypsin, hyaluronidase, elastase, elastase plus trypsin, or vehicle) can dissolve blood vessel walls, causing hemorrhage (Guth et al., 1980). Therefore, ChABC is a promising alternative therapy for promoting axonal plasticity in SCI, not only in the acute phase by preventing glial scar formation, but also in the chronic SCI phase through the digestion of the glial scar and promoting regeneration and functional recovery (Filous et al., 2010; Houle et al., 2006). Bradbury et al. (2002) showed, for the first time, the beneficial effects of ChABC on axonal regeneration and functional improvement after SCI. Despite the vast number of preclinical studies in this area (Filous et al., 2010; Houle et al., 2006; Massey et al., 2008), the exact mechanism of action is not known. However, much of the mechanism has been identified. Here, we systematically review the literature to summarize all potential histopathological effects of intrathecal administration of ChABC in spinal cord injured rats.

Materials and Methods

Our systematic review was conducted according to the PRISMA (preferred reporting items for systematic reviews and meta-analysis) 2020 checklist (Page et al., 2021).

Information sources and search strategy

We performed a comprehensive electronic search of studies published in PubMed, Scopus, Web of Science, Embase, and the Cochrane Library until November 22, 2021. We did not limit the search strategy by study type, language, or publication date.

Eligibility criteria, selection process, and data extraction

Two independent reviewers performed the screening, and the third reviewer resolved any discrepancies. The inclusion criteria were experimental animal studies on SCI models in adult rats that investigated intrathecal ChABC treatment. To explore the precise histopathologic effects of ChABC on the SCI recovery process, we limited our inclusion criteria to intrathecal administration of ChABC. We included a study if it had at least 2 intervention groups: 1 intrathecal ChABC treatment group and 1 control group (i.e. sham surgery or no treatment), and the study reported histopathological outcomes. According to the group's neurosurgeons' opinions, we preliminarily defined 5 histopathologic outcome groups as the most clinically relevant outcomes of interest, including:

1. Lesion breadth, also known as cavity volume, cyst size, myelin to cavity size ratio, or atrophic area.

2. Serotonergic (5HT) neurons' plasticity, defined as the total number of 5HT fibers crossing the lesion or the 5HT fibers' side branches in the lesion site.

3. Corticospinal tract (CST) plasticity, defined as the total number of CST fibers in the lesion site, CST fibers crossing the lesion site, or CST fibers' side branches in the lesion site.

4. Sensory neurons' plasticity, defined as the total number of sensory fibers in the lesion site, the number of sensory fibers crossing the lesion, or the sensory fibers' side branches in the lesion site.

5. Electrophysiological outcomes, defined by postsynaptic cord dorsum potentials (CDPs), the amplitude of action potential volleys, and neuronal conduction latency.

Studies included review articles, case reports, and case series. However, conference abstracts and posters without a published paper in a peer-reviewed journal were excluded. Also, we manually searched the references of the reviewed articles to identify any additional related articles.

Two independent reviewers performed the data extraction into the forms, and in the event of any discrepancy, a SCI specialist was consulted.

Risk of bias assessment

The risk of bias of the included studies was evaluated using the quality assessment tool for SCI animal models (Hassannejad et al., 2016) to assess pathophysiological events following traumatic SCI experiments. This assessment tool evaluates the studies regarding 15 domains: animal species, applying suitable tests, severity of the SCI, level of SCI, age/weight, experimental group sizes, description of strain, description of control groups, statistical analysis details, regulation of ethical issues, bladder expression, the blindness of measurements, genetic background, method of random allocation to experimental groups, and details of animal exclusions during the study.

If each column had no risk of bias, it was scored as positive "+," and if the presence of risk of bias was unclear due to insufficient descriptions in the article, it was scored as "–," and high risk of bias in each column was scored as negative. Differences in assessment were discussed during a consensus meeting. A total score was computed by adding the number of positive scores, and high quality was defined as fulfilling 8 or more (more than 50%) of the 15 internal validity criteria. Finally, the risk of bias for each included article was assessed using the data extraction form.

Results

A total of 3857 records were retrieved during database and bibliography searches, of which 2144 were unique after duplicates were removed. After screening by title and abstract, 1957 articles were excluded, and 187 papers were selected for full-text assessment. Of the 187 articles, 156 were excluded due to lack of intervention criteria (n=63), lack of a control group (n=1), conference abstracts without a peer-reviewed paper (n=38), review articles (n=2), and lack of histopathological outcome measures of interest (n=52). Seventeen studies (Barritt et al., 2006; Caggiano et al., 2005; Führmann et al., 2018; García-Alías et al., 2008; García-Alías et al., 2011; Ishikawa et al., 2015; Karimi-Abdolrezaee et al., 2010; Kim et al., 2006; Massey et al., 2008; Mountney et al., 2013; Pan et al., 2018; Shields et al., 2008; Shinozaki et al., 2016; Tom et al., 2009; Wang et al., 2011; Xia et al., 2015; Yang et al., 2009) were included in the qualitative analysis based on the following PICO criteria: (Figure 1) P, adult rats; I, intrathecal ChABC administration; C, sham surgery or non-treated injured animals; O, as entered in the method section. All included studies had a low risk of bias except one, which had a moderate risk of bias (Table 1).

All studies used adult rats, of which 11 studies used the Sprague Dawley (Führmann et al., 2018; García-Alías et al., 2011; Ishikawa et al., 2015; Kim et al., 2006; Massey et al., 2008; Mountney et al., 2013; Shields et al., 2008; Shinozaki et al., 2016; Tom et al., 2009; Xia et al., 2015; Yang et al., 2009), 3 the Wistar (Barritt et al., 2006; Karimi-Abdolrezaee et al., 2010; Pan et al., 2018), 2 the Lister hooded (García-Alías et al., 2008; Wang et al., 2011), and 1 the Long-Evans rats (Caggiano et al., 2005). Although all studies stated the size or number of the animals treated with ChABC and controls, only 7 mentioned the total number of animals sampled (a total of 440 rats) (Barritt et al., 2006; Führmann et al., 2018; Ishikawa et al., 2015; Karimi-Abdolrezaee et al., 2010; Pan et al., 2018; Shields et al., 2008; Shinozaki et al., 2016). The most common injury model in these articles was transection injury (García-Alías et al., 2008; García-Alías et al., 2011; Ishikawa et al., 2015; Kim et al., 2006; Massey et al., 2008; Pan et al., 2018; Shields et al., 2008; Tom et al., 2009; Wang et al., 2011; Xia et al., 2015). Compression injury (Caggiano et al., 2005; Führmann et al., 2018; Karimi-Abdolrezaee et al., 2010) and contusion injury (Barritt et al., 2006; Mountney et al., 2013; Shinozaki et al., 2016; Tom et al., 2009; Yang et al., 2009) were other injury methods. One study deployed both transection and contusion models (Tom et al., 2009). The size, level, and severity of the injury, as well as the injection time and whether unilateral or bilateral injury were used (Table 2).

The results, based on the phase of treatment, methodological details, and key findings of the included studies, are presented in Table 3. The treatment phase was defined as the time of ChABC administration (the first dose in multiple-dose regimens), and the studies were grouped as acute (within 24 hours after injury), subacute (5 or 7 days after injury), or chronic (4 or 6 weeks after injury). Four studies reported results of ChABC treatment on SCI lesion breadth (Caggiano et al., 2005; Führmann et al., 2018; Pan et al., 2018; Shinozaki et al., 2016). Eight studies evaluated the effects of ChABC treatment on serotonergic fiber plasticity and regeneration after SCI through anti-serotonin (5-hydroxytryptamine [5-HT]) immunostaining (Barritt et al., 2006; Ishikawa et al., 2015; Karimi-Abdolrezaee et al., 2010; Kim et al., 2006; Mountney et al., 2013; Shinozaki et al., 2016; Tom et al., 2009; Wang et al., 2011). CST remodeling after ChABC treatment was assessed in 12 studies (Barritt et al., 2006; García-Alías et al., 2008; García-Alías et al., 2011; Ishikawa et al., 2015; Karimi-Abdolrezaee et al., 2010; Kim et al., 2006; Massey et al., 2008; Shields et al., 2008; Shinozaki et al., 2016; Wang et al., 2014; Xia et al., 2015; Yang et al., 2009). Of the 17 studies, 8 used biotinylated dextran amine (BDA)-labeling for

Table 1. The risk of bias assessment of included studies

Author(s), Year	Species	Age/ Weight of the Animal Mentioned	Designation of Strain	Number of Samples/Per Groups	Level of Injury	Measuring the Severity of Injury	Consideration of Genetic Background	Method of Allocation to Intervention	Bladder Expression	Description of the Reasons to Exclude Animals from the Experiment during the Study	Regulation and Ethics	Definition of control Group	Using Appropriate Tests for the Evaluation of Outcome	Blindness of Assessor	Description of Statistical Analysis	Quality
Caggiano et al. (2005)	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	H(14)
Barritt et al. (2006)	+	+	+	+	+	+	+	+	-	-	+	+	+	-	+	H(12)
Kim et al. (2006)	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	H(13)
Massey (2006)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	H(15)
García-Alías et al. (2008)	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	H(14)
Shields et al. (2008)	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	H(12)
Tom et al. (2009)	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	H(13)
Yang (2009)	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	H(13)
Karimi-Abdolrezaee et al. (2012)	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	H(14)
Wang et al. (2011)	+	-	+	+	+	+	+	+	-	-	+	+	+	-	+	H(11)
García-Alías et al. (2011)	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	H(13)
Mountney et al. (2013)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	H(15)
Xia et al. (2015)	+	-	+	-	+	+	+	+	-	+	+	-	-	-	-	M(8)
Ishikawa et al. (2015)	+	+	+	-	+	+	+	-	-	+	+	+	+	-	+	H(11)
Shinozaki et al. (2016)	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	H(14)
Führmann et al. (2017)	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	H(13)
Pan et al. (2018)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	H(11)

H: High quality; M: Medium quality.

Note: No risk of bias: (+); the presence of risk of bias is unclear due to insufficient descriptions in the article or high risk of bias: (-).

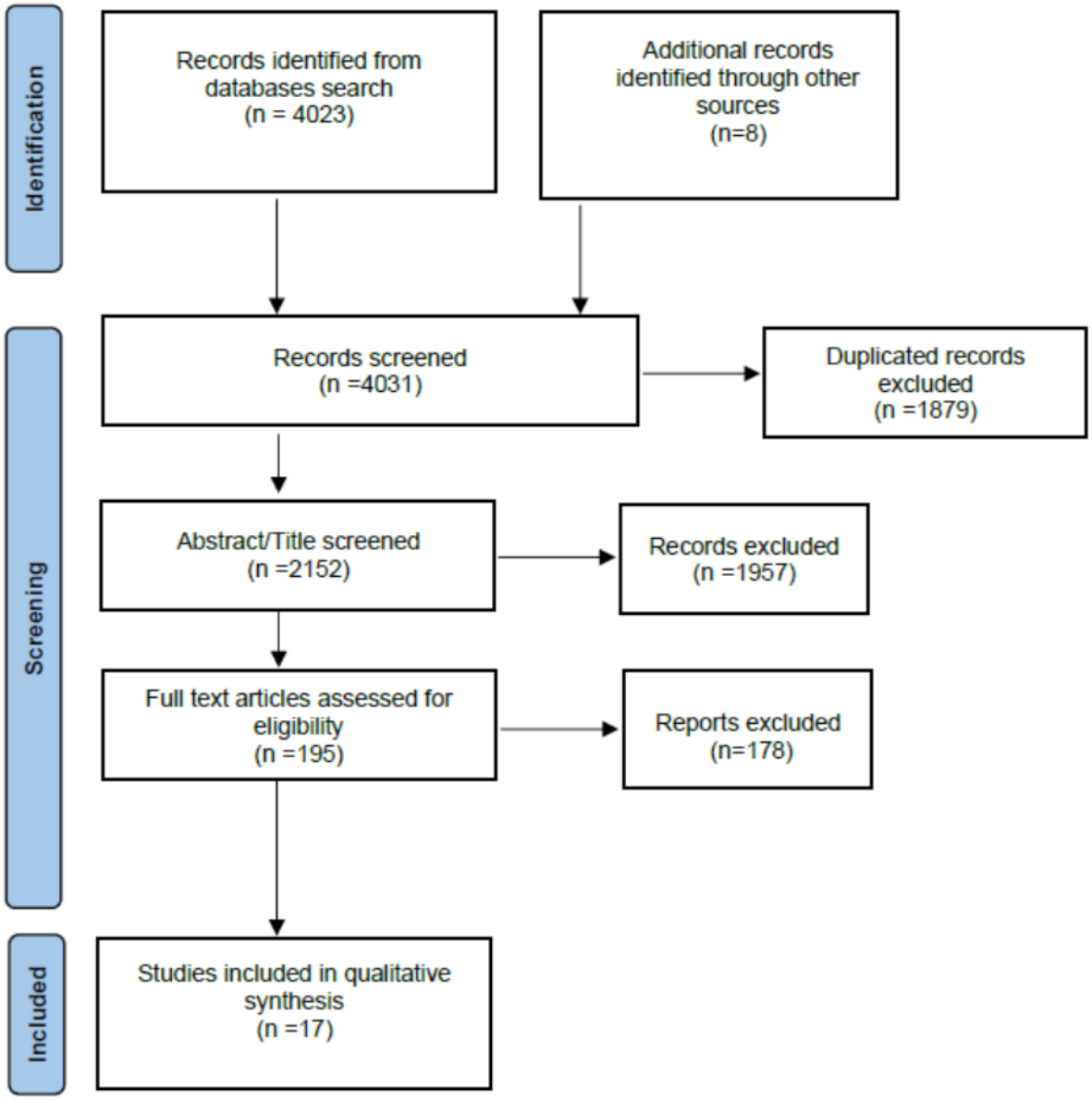

Figure 1. PRISMA flowchart diagram of the study process

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axonal tracing (Barritt et al., 2006; García-Alías et al., 2008; García-Alías et al., 2011; Karimi-Abdolrezaee et al., 2010; Kim et al., 2006; Wang et al., 2011; Xia et al., 2015; Yang et al., 2009), one used WGA labeling (Shinozaki et al., 2016), and another used protein kinase C-γ (Ishikawa et al., 2015). Two high-quality studies used cholera toxin B-subunit (CTB) labeling in the acute SCI model to assess the potential effects of ChABC treatment on sensory neurons (Massey et al., 2008; Shields et al., 2008). The other study used calcitonin gene-related peptide (CGRP) immunohistochemistry (Barritt et al., 2006). Again, 2 other high-quality studies reported electrophysiological outcome measures of interest (García-Alías et al., 2011; Yang et al., 2009).

Acute phase

Lesion breadth

One study used transection injury models (Pan et al., 2018), and two used compression (Caggiano et al., 2005; Führmann et al., 2018) to report the effects of acute ChABC administration on lesion breadth. In transection and contusion models, ChABC administration significantly decreased lesion length, cyst length at the injury site, hole size, and atrophic area volume (Pan et al., 2018; Shinozaki et al., 2016). However, acute administration of ChABC did not change the lesion length in the compression injury model.

Plasticity of serotonergic neurons

Two studies used transection injury models (Ishikawa et al., 2015; Kim et al., 2006), two studies used contusion (Barritt et al., 2006; Mountney et al., 2013), and one study used both transection and contusion models (Tom et al., 2009) to assess the effects of acute ChABC administration on serotonergic neuron plasticity. In transection models, ChABC increased the number of serotonergic fibers at the injury site and rostral part of the injury, but it had a weak effect on reaching the caudal sites. In contusion injury models, treatment positively affected the ventral caudal horn in contrast to the caudal dorsal horn, where it did not change.

Plasticity of corticospinal neurons

Four studies used transection injury models (García-Alías et al., 2008; Kim et al., 2006; Wang et al., 2014; Xia et al., 2015), and 2 used contusion (Barritt et al., 2006; Yang et al., 2009) to assess changes in CST neuron plasticity in response to acute ChABC administration. In transection models, treatment increased the number of CST fibers and their rostral length, but results were inconsistent at the injury site and in the caudal regions. Axonal sprouting was also increased at the injury site. One of two contusion studies reported increased CST fiber growth into and beyond the injury site, as well as increased terminal arborization (Barritt et al., 2006). In contrast, the other study (Yang et al., 2009) reported no difference in fiber length or number. The only compression study reported increased fiber growth and sprouting at the injury site and in the caudal regions (Führmann et al., 2018). To improve conduction, more studies on contusion and compression models are warranted.

Plasticity of sensory neurons

One study used transection injury models (Shields et al., 2008), and another used both compression and contusion models (Barritt et al., 2006). Both studies observed that acute administration of ChABC promoted afferent fiber plasticity and growth into and beyond the injury site. However, none of the included studies evaluated electrophysiological outcomes during the acute phase.

Subacute phase

Lesion breadth

Two studies that used compressive injury models (Caggiano et al., 2005; Führmann et al., 2018) reported effects of ChABC subacute administration on lesion breadth, showing weak positive effects. Concerning the other outcome of interest, we found no studies reporting on the evidence for the effect of ChABC administration on serotonergic, sensory, and corticospinal neuronal plasticity.

Chronic phase

Lesion breadth

Only 1 contusion injury study (Shinozaki et al., 2016) assessed lesion breadth changes in response to chronic administration of ChABC and found no influence of its treatment on lesion breadth changes. However, two studies reported increased tissue or axonal preservation with this treatment, either treadmill rehabilitation (Shinozaki et al., 2016) or neural progenitor cell transplantation (Karimi-Abdolrezaee et al., 2010).

Serotonergic neurons' plasticity

Chronic administration of Ch-ABC significantly increased the number and length of serotonergic fibers and sprouting at the rostral epicenter and caudal side of the lesion site (Karimi-Abdolrezaee et al., 2010; Shinozaki et al., 2016).

Corticospinal neuron plasticity

Chronic administration of ChABC significantly increased CST axon crossing and sprouting and rostral regrowth length (Karimi-Abdolrezaee & Billakanti, 2012; Karimi-Abdolrezaee et al., 2010; Shinozaki et al., 2016), but in caudal regions, there was no consensus on treatment effects. Two of the included studies (Karimi-Abdolrezaee & Billakanti, 2012; Shinozaki et al., 2016) reported no effects in the caudal regions. Overall, none of the included studies evaluated electrophysiological outcomes during the chronic phase.

Functional outcome

Most studies used the Basso, Beattie, Bresnahan (BBB) scale (for hindlimb), ladder walk test/staircase reaching test, grid-walking/strength test, hindlimb contact placing response/vertical exploration (rearing) and sticker removal tests (for forelimb function), single pellet reaching task, fine touch and mechanical hyperalgesia assessment, spinal cord evoked potential and motor evoked potential assessment to evaluate motor and sensory functional outcomes (Caggiano et al., 2005; Führmann et al., 2018; García-Alías et al., 2008; García-Alías et al., 2011; Ishikawa et al., 2015; Kim et al., 2006; Mountney et al., 2013; Pan et al., 2018; Shinozaki et al., 2016; Tom

Table 2. Study characteristics

Author(s), Year	Animal Strain	No. of Rats	Gender/ Age/ Weight	Sample Size	Injury Model/ Treatment Phase Group	Injury Model	Injection Time (S)	Injury Level	Uni-or Bi-Lateral Injury	Size of Injury	Injury Severity
Caggiano & Fehlings (2005)	Long-Evans rats	N.S	Female - -	ChABC I (severe: 10, moderate: 19, Mild: 15) Penicillinase control (Severe: 10, moderate: 19, mild: 15)	Acute compression	Compression	Immediately after SCI + every other day for 2 weeks	T9-T10	Bilateral	0.9-1.3 mm	Mild Moderate Severe
Barritt et al. (2006)	Wistar rats	82	Male adult 200-250 gr	ChABC (n=16) Vehicle control (n=16)	Acute contusion	Contusion	Immediately after SCI and subsequent injections on days 2, 4, 6, 8, and 10	C4	Bilateral	2 mm	Moderate
Kim et al. (2006)	Sprague Dawley rats	N.S	Female 2-3 months 200-250 g	ChABC (n=7) Penicillinase (n=7) Control (n=5)	Acute transection	Hemi-transection	Immediately after SCI + 3, 7, and 11 days after SCI	Cervical	Unilateral: The entire right side of the cord plus the left dorsal column and adjacent gray matter	N.S	Destruction of more than two-thirds of the transverse area of the cervical spinal cord
Massey et al. (2006)	Sprague Dawley rats	N.S	Male adult 250–300 g	ChABC (n=6) Penicillinase control (n=5)	Acute transection	Transection	Immediately after SCI	C6–C7	Unilateral: from the lateral portion of the right side of the dorsal spinal cord, through the right dorsal horn, and into the left gracile fasciculus	1.5 mm	A 1.5-mm deep dorsal-to-ventral laceration
García-Alías et al. (2008)	Lister Hooded rats	N.S	- - 250–300 g	ChABC 6 (acutely after the spinal cord injury) ChABC 6 (2 days (G2) after the injury) ChABC 6 (4 days (G4) after the injury) ChABC 6 (7 days (G7) after the injury) Penicillinase control 6 (acutely after the spinal cord injury)	Acute transection Subacute transection	Hemi-transection	Refer to column D	C4	Bilateral	2 mm	Complete cut 2 mm in depth into the spinal cord parenchyma

Author(s), Year	Animal Strain	No. of Rats	Gender/ Age/ Weight	Sample Size	Injury Model/ Treatment Phase Group	Injury Model	Injection Time (S)	Injury Level	Uni-or Bi-Lateral Injury	Size of Injury	Injury Severity
Shields et al. (2008)	Sprague Dawley rats	22	Female adult 200-225 g	ChABC low dose (n=8) ChABC High dose (n=9) Penicillinase control (n=5)	Acute transection	Hemi-transection	Immediately after SCI + alternate days for a total of 5 injections (days 0,2, 4, 6, and 8)	C3	Unilateral	3.6 mm (blade)* 1.5 mm deep	Complete cut 1.5 mm deep
Tom et al. (2009	Sprague Dawley rats	N.S	Female adult 250-225 g	ChABC (hemisection, rostral tx) (n=8) ChABC (hemisection, caudal tx) (n=8) ChABC (hemicontusion) (n=8) PBS controls (n=22)	Acute transection Acute contusion	Hemi-transection Hemi-contusion	Immediately after SCI	C5	Unilateral	2-3 mm	1- Complete transection 2-200 kdyne force with a displacement of tissue to a depth of 1600–1800 mm
Yang et al. (2009)	Sprague Dawley rats	N.S	Male and female adult 180-250 g	ChABC (n=36) Saline control (n=36)	Acute contusion	Contusion	30 minutes after SCI	T8 – T10	N.S	3 mm	A 10 g rod, 3 mm in diameter and 100 mm in length, was dropped onto the exposed spinal cord surface.
Karimi-Abdolrezaee et al. (2010)	Wistar rats	165	Female adult 250 g	ChABC (number not specified) Penicillinase control (number not specified)	Chronic compression	Compression	6 weeks after SCI	T7	N.S	N.S	23 g clip (Walsh) compression injury for 1 min
Wang et al. (2011)	Lister hooded rats	N.S	Male - 150–200 g	Ch-ABC (n=10) Penicillinase control (n=10)	Chronic transection	Transection	One month after the SCI, a total of five injections were administered once every 2 days following surgery.	C4	Bilateral	2 mm	Complete transection
García-Alías et al. (2011)	Sprague Dawley rats	N.S	Female adult 200 g	ChABC 22 Uninjured control 6 Sham control 6	Acute transection	Hemi-transection	Immediately after SCI	T8	Unilateral (left hemicord transection)	N/A (left hemicord was transected completely)	Complete transection

Author(s), Year	Animal Strain	No. of Rats	Gender/ Age/ Weight	Sample Size	Injury Model/ Treatment Phase Group	Injury Model	Injection Time (S)	Injury Level	Uni-or Bi-Lateral Injury	Size of Injury	Injury Severity
Mountney et al. (2013)	Sprague Dawley rats	N.S	Female adult 250–375 g	ChABC (n=10) Carrier control (n=12)	Acute contusion	Contusion	Immediately after injury	T9	Bilateral	1.2–0.1 mm	Moderate (200 kdyne)
Xia et al. (2015)	Sprague Dawley rats	N.S	Female - 250-300	ChABC (n=6) Saline control (n=6) Sham (n=6)	Acute transection	Transection	Immediately after injury	T9-T10	Uni-lateral	1.8 mm	Severe
Ishikawa et al. (2015)	Sprague Dawley rats	58	Female Adult 200-250 g	ChABC (n=5) Uninjured Control (n=3) Sham control (n=5)	Acute transection	Transection	Immediately after SCI	C3-C4	Uni-lateral	2 mm	Complete a cut 2 mm in depth in the spinal cord.
Shinozaki et al. (2016)	Sprague Dawley rats	61	Female adult 200–220 g	ChABC (5HT, cavity) (n=7) Vehicle control (n=8) Ch-ABC (CST) (n=3) Vehicle control (n=5)	Chronic contusion	Contusion	T10	Six weeks after SCI	N.S	N.S	Severe (250 kdyn)
Führmann et al. (2017)	Sprague Dawley rats	60	Female adult 300 g	Ch-ABC (n=11) Vehicle control (n=11)	Subacute compression	Compression	One week after SCI	T1-2	Bilateral	Not mentioned exactly. Approximately ~1 mm	21 g modified aneurysm clip for 1 min (moderate)
Pan et al. (2017)	Wistar rats	50	Female average 10 weeks average 250 g	ChABC (n=12) Sham control (n=6) NaCl/saline control (n=8)	Acute transection	Transection	Immediately after SCI	T10	Uni-lateral	2 mm	Complete transaction

Abbreviations: N.S: Not specified; ChABC: chondroitinase ABC; SCI: Spinal cord injury.

et al., 2009; Wang et al., 2011; Xia et al., 2015; Yang et al., 2009). Also, one study used residual urine volumes to test for autonomic functions (Caggiano et al., 2005). Overall, the functional outcome were mixed, with 3 studies showing no improvement in functional outcomes after ChABC administrations (Führmann et al., 2018; Mountney et al., 2013; Tom et al., 2009) and 9 showing that ChABC administration alone (García-Alías et al., 2008) or combined with neurotrophin NT-3 secretion and NR2D expression (García-Alías et al., 2011) or NPCs (Karimi-Abdolrezaee et al., 2010), or antisense vimentin cDNA (Xia et al., 2015) or poly(glycerol sebacate) (Pan et al., 2018) or insulin+ methylprednisolone (Yang et al., 2009) or transplant mediated axonal remodeling or rehabilitation (Ishikawa et al., 2015; Shinozaki et al., 2016; Wang et al., 2011) improved functional outcomes, particularly motor functions (Table 3).

Discussion

SCI is a devastating clinical condition that results in rapid-onset and long-term disability related to the central nervous system. Several underlying mechanisms have been identified as factors responsible for primary and secondary damage following SCI. Primary mechanisms include neural death and axonal injury, which subsequently lead to sensorimotor disruption (de Almeida et al., 2023). After the primary complications, secondary mechanisms are initiated, including inflammation, vascular changes, ion disproportion, glutamate excitotoxicity, and radical formation, which result in additional complications, including progressive neural death, edema, hyperpyrexia, and paralysis (de Almeida et al., 2023; Korovessis, 2019). Inflammation and granulocyte colony-stimulating factor (G-CSF) production are two major components of glial scar formation that hamper recovery after SCI (Shechter et al., 2011). A correlation between inflammation and G-CSF expression via inflammatory cytokines has been reported in the literature (Shechter et al., 2011). The evidence suggests that inflammatory cytokines enhance GSK3β expression, which, in turn, promotes demyelination and neuronal degeneration (Nagai et al., 2016; Renault-Mihara et al., 2011). Furthermore, GSK3β may prevent post-SCI neuronal regeneration by modulating G-SCF discharge (Nagai et al., 2016). Therefore, therapeutic agents are designed to disrupt the molecular mechanisms underlying complications related to SCI.

Although several therapeutic approaches, including pharmacological, stem cell-based, and enzyme-based approaches, have been developed for SCI, the management of patients with SCI remains challenging in developing or even developed countries. The difficulty in treating SCI patients is related to environmental factors in the injured area (de Almeida et al., 2023). However, advances in understanding SCI pathology have led to de novo research into new treatment approaches. Recent studies have focused on the secondary mechanisms involved in SCI to prevent further damage and facilitate neural regeneration. Kwon et al. (2011a) systematically reviewed the pre-clinical studies of neuroprotective agents already prescribed in humans. This study documented the potential effect of non-invasive medications for acute SCI, including erythropoietin, progesterone, estrogen, riluzole, polyethylene glycol, atorvastatin, magnesium, minocycline, inosine, NSAID, anti-CD11, and pioglitazone. In 2010, Cadotte and Fehlings, highlighted the effects of riluzole, anti-Rho antibody, and surgical decompression on SCI, thereby establishing evidence for translating preclinical research into clinical research (Cadotte & Fehlings, 2011).

In 2011, another systematic review by Kwon et al. (2011b) aimed to investigate in vivo studies on the efficacy of intraspinal ChABC, anti-Nogo antibody, and anti-Rho antibody strategies, providing evidence for translating preclinical findings into human studies and clinical trials. They found that the Nogo receptor on neural cells prevents neural growth, suggesting that an anti-Nogo antibody is a promising therapeutic approach to promote neural recovery following SCI. Also, clinical trials have been conducted to investigate the effects of anti-Nogo in patients with acute and chronic SCI. Additionally, although riluzole is a sodium glutamate antagonist used in patients with amyotrophic lateral sclerosis (ALS), it is a potential drug for SCI patients due to its neuroprotective effect. A recent systematic review of the efficacy of riluzole in SCI, including animal and human studies, showed that riluzole is also a promising pharmacological agent that improves behavioral outcomes, promotes histological sparing, and exhibits electrophysiological effects following SCI, while diminishing the sequelae of this condition (Srinivas et al., 2019).

Several key components, such as inflammation, oxidative stress, and edema, have been considered in the pathophysiology of SCI and can inform the development of effective therapeutic modalities. For instance, oxidative stress is putatively involved in the secondary deterioration of SCI. Therefore, depletion of reactive oxidative stress could be an effective approach to prevent SCI-associated secondary deterioration in patients. Medications, including the glucocorticoid steroid and the non-glucocorticoid 21-aminosteroid tirilazad, also have antioxidant activity that significantly enhances re-

Table 3. Chondroitinase ABC treatment phase, the details of methodological information, histopathological, and functional outcomes

Author(s), Year	Tracing of CST Axons	Injection Dose	Injection Details	Injection Site + Device	Histopathological Findings	Functional Outcomes
Caggiano et al. (2005)	N.S	0.06 units (defined as the quantity of the enzyme that catalyzes the formation of 1 mole of unsaturated disaccharide from chondroitin-6-sulfate per minute at 37 °C, pH 8.0) per rat per dose	5 µL of ChABC-XMC+ 7 days following clip compression injury and ChABC-XMC, 5 µL of ChABC-XMC (or XMC or buffer) was intrathecally injected through a 30-gauge angled blunt-tipped needle	Into the intrathecal space through a 30-G angled blunt-tipped needle	1. No obvious qualitative effect on injury length and breadth in different compressive injury severities for chondroitinase treatment	ChABC I treatment demonstrated improvements in both somatic motor and autonomic function: animals treated with ChABC I scored higher on the BBB scale (>8), indicating consistent sweeping of the legs or paw placement, and some showed some degree of weight support. Regarding autonomic functions, residual urine volumes from the severely injured control group returned to approximately 4–6 mL per day, while residual volumes in the ChABC-treated rats declined to approximately 2 mL per day (Fig. 8). This finding was similar for ChABC-treated rats with moderate injury; ChABC treated rats and controls with mild injury showed no significant difference regarding residual urine volume.
Barritt et al. (2006)	Biotinylated dextran amine (BDA; 10000 MW; Invitrogen, Eugene, OR)	10 U/mL. 6 µL	0.06 Units (defined as the quantity of the enzyme that catalyzes the formation of 1 mole of unsaturated disaccharide from chondroitin-6-sulfate per minute at 37 °C, pH 8.0) per rat per dose, in artificial cerebrospinal fluid (aCSF: cat. No. 58-7316, lot No. 111261; Harvard Apparatus, Holliston, MA)	Intrathecally (i.t.) + A 32-gauge catheter (cat. No. CS132G, lot No. 20422; ReCathCo, LLC, Allison Park, PA) with chondroitinase ABC I (cat. No. 100332, lot No. E02201; Seikagaku, Associates of Cape Cod, Falmouth, MA) was inserted through the dural incision and fed rostrally to lay immediately caudal to the T9/T10 laminectomy.	1. Chondroitinase ABC promotes the sprouting of serotonergic fibers ventral and caudal to a spinal cord injury 2. Chondroitinase treatment confirmed a significant increase in CST fibers' density compared to the vehicle group. 3. Chondroitinase ABC promotes sprouting of the corticospinal tract rostral, within, and caudal to a spinal cord injury 4. Chondroitinase treatment significantly promotes CGRP+ afferents' plasticity caudally to a lesioned spinal cord. 5-Treatment with ChABC robust sprouting also occurred ventral to the injury site, with intense immunoreactivity and numerous sprouting fibers apparent in the ventral columns 6-Lesioned animals treated with ChABC had significantly increased intensity of PKC immunoreactivity	N.S

Author(s), Year	Tracing of CST Axons	Injection Dose	Injection Details	Injection Site + Device	Histopathological Findings	Functional Outcomes
Kim et al. (2006)	The number of axons that are labeled by BDA	0.2 U of ChABC in 20 L vehicle solution (0.1% bovine serum albumin in saline) was applied with gel foam	10 µL of 100 U/mL	N.S	1- Remodeling of corticospinal axons is not affected by the degradation of CSPGs. 2- Raphespinal axon remodeling is promoted by ChABCase treatment following transplantation 3- Increase of serotonin immunoreactive fibers in rats treated with ChABC 4- ChABC greatly decreased the CS-56 immunoreactivity 5- ChABC increases in 2B6 immunoreactivity	Chondroitinase ABC, in combination with transplantation, improved fine control of the distal forelimb and skilled motor functions, such as sticker removal and grid walking.
Massey et al. (2006)	5–10 µL of 1% CTB (Sigma-Aldrich, St. Louis, MO), dissolved in 0.25 M Tris–HCl, pH 7.4	1 µL of 50 U/mL	1.96×10^{6} TU/µL/0.5 µL each injection	3 injection sites: at the lesion epicenter, 0.5 mm rostral, and 0.5 mm caudal to the lesion epicenter, with 2 injection depths: 1.2 and 0.6 mm from the dorsal surface	1- When the brainstems of ChABC-treated injured rats were examined, the CTB-immunoreactive forepaw terminal area was significantly greater compared with that of the P-ase-treated injured rats 2- ChABC reduced the CSPG 3- Significantly increased number of neurons	N.S
García-Alías et al. (2008)	1 µL of 10% BDA solution in 0.01 M phosphate buffer		6 µL. 100 U/mL per injection		Every animal received a total of six injections, of chondroitinase (6 µL, 100 U/mL per injection) or penicillinase (6 µL, 100 U/mL per injection), one every two days following the first injection.	
Shields et al. (2008)	CTB (1% in distilled water; List Biological Laboratories Inc, Campbell, CA)	0.18 units per 6 µL (high dose). low-dose 0.06 units/6 µL	6 mL ChABC (10 U/mL 21) was injected, followed by a 6 mL saline flush (n=17). A further group received the spinal cord lesion with either saline or control enzyme treatment (Penicillinase, Sigma; same mg protein delivered, n=21).	Intrathecally inserted to lie just rostral to the lesion site, and externalized to deliver bolus injections of high-purity, protease-free Chondroitinase ABC (ChABC; Seikagaku Corporation). 6 mL ChABC (10 U/mL 21) was injected, followed by a 6 mL saline flush (n=17). A further group received the spinal cord lesion with either saline or control enzyme treatment (Penicillinase, Sigma; same mg protein delivered, n=21). ChABC or control solution + a silastic tube	1- Chondroitinase treatment caused a significant dose-dependent increase in sensory neurons' axonal number (2.1-fold low dose, 3.1-fold high dose vs control group) and axonal length (8.3-fold low dose, 9.9-fold high dose vs control group) 2- Increase the number of axons growing into the scar 3- CSPG, NG-2 and CS-56 expression were decreased 4- 2-B-6 expression was increased 5- ChABC infusion did not influence laminin and GFAP	N.S

Author(s), Year	Tracing of CST Axons	Injection Dose	Injection Details	Injection Site + Device	Histopathological Findings	Functional Outcomes
Tom et al. (2009)	N.S	10 µL. 50 U/mL	For infusion, an enzyme aliquot (0.33 mg/mL (5 units/mL) (200 µL) was loaded into the reservoir of an Alzet 2004 osmotic minipump	After stereotaxic implantation of the infusion tip through the T9 vertebra, 1.3 mm into the thoracic cord, and 0.5 mm from the distal interface, the infusate was delivered at 0.5 µL/h from the loaded mini pump	1- Chondroitinase treatment leads to significantly greater preservation of serotonergic fibers rostral to the hemisection injury site, but not caudally. 2- Chondroitinase treatment leads to significantly more serotonergic fibers' preservation in the ventral horn of the caudal site of the hemi-contusion injury site 3- Increased 5 HT+ fiber sprouting	No functional improvement. The study concluded that although administering ChABC rostral or caudal to a unilateral spinal cord injury is sufficient to promote plasticity in supraspinal fiber populations, this plasticity does not appear to have functional ramifications. Their data demonstrated that sprouting rostral or caudal to a spinal cord injury does not always translate to recovery and indicates that other mechanisms may be responsible for ChABC-mediated functional recovery.
Yang et al. (2009)	1 µL biotinylated dextran amine (BDA) (BDA-3000, Molecular Probes, Eugene, OR, USA) for 20 min.	6 µL ChABC. 10 U/mL	0.05 U/200 µL	A thin silicone tube with an osmotic minipump (Model 2006; ALZET, Cupertino, CA; 200 µL of the solution, 0.5 µL/h, 14 d delivery) into the subarachnoid cavity, and set the tube tip at the C3 level under a surgical microscope	1- More nerve fibers and longer axons were found in rats treated with insulin, insulin plus ChABC, or methylprednisolone than in rats of the other two groups 2- Lower apoptosis in rats treated with Ch-ABC 3- More GAP-43 positive cells in rats treated with ChABC	At 4 weeks after spinal cord injury, the rats in the insulin, insulin plus ChABC, or methylprednisolone groups could walk normally. Still, the control rats and those treated with ChABC alone could not. From 0 to 2 weeks after injury, SCEP in rats treated with insulin, insulin plus ChABC, or methylprednisolone gradually recovered in latency and amplitude. From 1 to 2 weeks after injury, MEP latency and amplitude at the proximal site gradually recovered in rats treated with insulin, insulin plus ChABC, or methylprednisolone.
Karimi-Abdolrezaee, & Billakanti (2012)	BDA (10%, 10000 MW; Invitrogen) was injected unilaterally into the left sensorimotor cortex at eight sites (0.5 µL per site)	5 U/mL of ChABC in saline plus 0.1% rat serum albumin	Seikagaku, 5 U/mL in saline plus 0.1% rat serum albumin) was administered intrathecally using a catheter (Alzet, Rat IT, 0007741, 0.36 mm outer diameter [OD]; 0.18 mm inner diameter [ID]) connected to an osmotic minipump (Alzet pump model No. 1007D, 0.5 l/h) for 7 d. The animals underwent intraspinal bilateral injections of NPCs or vehicle with 8 µL of cell suspension, containing 4×10^5 live cells, which was intraspinally injected into the dorsolateral spinal cord, next to the midline	The catheter was inserted into the subarachnoid space around the injured area. One week after ChABC or vehicle treatment (7 weeks after SCI), the animals underwent intraspinal bilateral injections of NPCs or vehicle. Four intraspinal injections were bilaterally made at a point 2 mm rostral and 2 mm caudal to the injury site.	1- ChABC treatment at 6 weeks after injury for 1 week resulted in a pronounced reduction in CSPGs in the perilesional areas compared to the vehicle treatment. 2- At 3, 6, and 9 weeks after transplantation, we found a striking increase in the number of surviving YFP-NPCs in the ChABC-treated group compared to the vehicle-treated group. 3- ChABC treatment induced CSPG degradation, resulting in promoting the survival and integration of engrafted NPCs 4- ChABC and NPC transplantation promote axonal preservation and sprouting of the CST axons rostral to the lesion. 5- ChABC treatment and NPC transplantation promote serotonergic fiber plasticity by increasing 5-HT expression in the spinal cord. 6- ChABC, GF, or NPC showed no significant changes in the injury-induced pattern of sprouting in CGRP afferents in laminae III–V after treatments	ChABC treatment and NPC transplantation improve locomotor function after chronic SCI, with particular emphasis on rats treated with the combination of ChABC/GFs+NPCs, who regained their pretreatment BBB scores at 2 weeks after NPC transplantation and then showed progressive improvement in their scores over time. Also, statistically significantly greater frequency of consistent weight-supported plantar steps and evidence of forelimb–hindlimb coordination in the ChABC/GF+NPC group than in other groups from weeks 5 to 8 after transplantation was observed. Regarding neuropathic pain, no increased sensitivity to thermal stimulation was detected among any of the experimental groups after treatments.

Author(s), Year	Tracing of CST Axons	Injection Dose	Injection Details	Injection Site + Device	Histopathological Findings	Functional Outcomes
Wang et al. (2011)	BDA (10% w/v, MW 10000, Invitrogen)	1 µL. 100 U/mL	Chondroitinase ABC I (Seikagaku), 0.06 U/dose (240 µg per mL), i.t. (intrathecally) in 3 µL aCSF.	Animals were treated intrathecally (i.t.) with Chondroitinase ABC I	1- More CST fibers' crossing and sprouting. 2- More serotonergic fibers sprouting. 3- No effect on sensory neurons. 4- An increase in the number of 5-HT axons, ChABC had significantly more Biotinylated dextran amine, vGlut1 synaptic puncta	ChABC induced functional recovery in chronic SCI when paired with task-specific rehabilitation. 1. Animal groups that received Ch-ABC and rehabilitation achieved six pellets eaten on average (±1.52), compared with the other three groups, which reached 0.5± 0.40 (Pen alone, P <0.001), 0.56±0.29 (Ch-ABC alone, P< 0.001), and 2.3±0.58 (Pen rehab, P< 0.001) pellets eaten (Fig. 4a). 2. Animals in the Ch-ABC rehab group also showed greater accuracy on the staircase apparatus compared with other groups (Fig. 4b)
García-Alías et al. (2011)	1 µL of 10% BDA in the gigantocellular nucleus of the reticular formation under sterile conditions	1 µL. 100 U/mL	ChABC (Seikagaku, 5 U/mL in saline plus 0.1% rat serum albumin	23 g clip (Walsh) compression injury for 1 min at the level of T7 of the spinal cord	1- Animals receiving chondroitinase have significantly more sprouting and more axon crossing than the penicillinase group. 2- Chondroitinase, in contrast to the penicillinase group, led to a small EPSP (amplitude 0.82±0.35 mV; latency 5.4±0.5 ms) in contralateral stimulation. No EPSP was seen in ipsilateral stimulation.	ChABC-treated animals in all groups showed substantial improvements with most of the gait measures returning almost to normal as compared to the PEN animals
Mountney et al. (2013)	N.S	2 U/mL, 6 µL	An injection of 6 µL of only ChABC (10 U/mL)	Injection into the subarachnoid cavity under the section (was injected once into the subarachnoid cavity under the section according to Barritt et al. 30	1- Ch-ABC treatment did not increase 5-HT/serotonin axon immunostaining compared with controls 2- ChABC-treated rats did not have increased GM1 and GT1b staining	ChABC alone and sialidase/ChABC combination-treated animals did not show enhanced improvement in hindlimb motor and sensorimotor functions over the final 2 weeks of the testing compared with control-treated rats
Xia et al. (2015)	2 µL 10% solution of BDA (10,000 molecular weight, lysine fixable; Molecular Probes, Eugene, OR) into the three sites in the motor cortex	6 µL. 10 U/mL	6 µL of cABC (10 U/m)		1- Chondroitinase treatment caused some CST axons to regrow into and beyond the injury site caudally	Most ChABC-treated animals (5/6) regained hind limb placing response. Also, combined-treatment rats had higher BBB scores than single-treated rats.

Author(s), Year	Tracing of CST Axons	Injection Dose	Injection Details	Injection Site + Device	Histopathological Findings	Functional Outcomes
Ishikawa et al. (2015)	Protein kinase C-γ (1:500)	200 µL. 0.05 U/mL	Chondroitinase ABC was obtained from Sigma-Aldrich (St. Louis, MO) (C3667) and was pure, protease-free, and supplied in vials (0.5 mg = 5.15 units). Each injection of Ch-ABC was freshly prepared on the day of administration. Saline (167 µL) was added to each vial, creating a solution of 0.18 units per 6 µL (high dose). The low-dose solution was formulated by diluting this to 0.06 units per 6 µL. High-dose Ch-ABC (0.18 units/treatment, n = 9) and low-dose Ch-ABC (0.06 units/ treatment, n = 8) was injected.	An IT injection through the catheter was placed via a dural opening at C4-5 (Fig. 1A) and threaded rostrally in the SAS. A polyethylene (PE-10) catheter (Becton Dickinson, Sparks, MD) was used. The PE-10 tubing was heated and tapered to obtain a 100-µm OD at its tip. The entire catheter (80 mm long) contained 3 µL of volume.	1- Chondroitinase treatment caused a trend toward an increase in serotonergic fibers' regrowth, but it was not significant 2- Ch-ABC significantly increased the Gap-43 and 5-HT positive fibers	The combination of rehabilitation and KS- or CS-digestion resulting from ChABC treatment tended to achieve better recovery than rehabilitation and saline alone, but the difference was not significant.
Shinozaki et al. (2016)	CST fibers were labeled with Alexa Fluor 488-conjugated wheat germ agglutinin (WGA) (1.0% in saline, 4.0 µL/cortex; Invitrogen)	40 U/200 µL, 1 µL	In the ChABC group: 6 µL ChABC and 6 µL of saline were given on each of the subsequent 6 days.	The tail was connected to a microinjector tube after spinal cord injury	1- ChABC treatment increased serotonergic fibers significantly rostrally, and at the lesion epicenter, and caused some fibers to traverse the lesion and reach the caudal site (rostral-1.6 mm, rostral-0.4 mm, epicenter, caudal-0.4 mm, caudal-0.8 mm, caudal-2 mm) 2- More WGA-labeled CST fibers reached the lesion epicenter in the ChABC group vs the vehicle group, but no one reached caudal sites. (Rostral-5.0 mm, rostral-2.0 mm, rostral-1.0 mm, epicenter) 3- Significantly lower CSPG content in the ChABC group 4- The RT-97-positive area caudal was significantly increased 5- Increase the GAP-43 positive area 6- The fibers reached closer to the epicenter in the ChABC group	The ChABC group demonstrated a third recovery phase at 12–14 weeks after SCI and showed significant differences in final BBB scores compared with the no-treatment control group (F 2, 23 =3.81, n=24, P=0.039). This finding signifies that combinatorial ChABC/rehabilitation therapy delivered an improved functional outcome compared to rehabilitation alone, with significantly increased locomotor scores (ie, improved motor functions)

Author(s), Year	Tracing of CST Axons	Injection Dose	Injection Details	Injection Site + Device	Histopathological Findings	Functional Outcomes
Führmann et al. (2017)	N.S	5 µL. 100 U/mL	1 µL of 50 U/mL P-ase or Ch-ABC was injected	In animals receiving enzyme treatments after SCI, the right medulla was exposed immediately after the injury, and 1 µL of 50 U/mL P-ase or ChABC was injected at 0.5– 0.3 mm below the dorsal pial surface and just lateral to the cuneate nucleus.	1- ChABC tends to decrease cystic cavitation and lesion volume, but it was not significant. 2- ChABC significantly decreased the expression of CSPG 3- Increase the differentiation of neural stem cells to differentiated neurons	Treatments did not influence the behavioral outcome at 9 weeks post-injury in that, compared to uninjured animals, animals that underwent compression injury showed a drop in animal motor function‡
Pan et al (2017)	N.S	6 µL. 10 U/mL	1 µL injection of ChABC (100 U/mL, protease-free, Seikagaku). The animals received a total of five injections of ChABC through the cannula (3 l, 100 U/mL per injection, Acorda Therapeutics) or Pen (3 µL, 100 U/mL per injection), once every 2 days following surgery.	Intrathecally insertion through the opening of the cisterna magna, with the tip lying on top of the injury of ChABC through the cannula (3 l, 100 U/mL per injection, Acorda Therapeutics) or Pen (3 l, 100 U/mL per injection) + A 32-gauge catheter (ReCathCo)	1- Big holes in the transection region of the spinal cords were seen in rats of the control group; small holes, breaks, and cysts were observed in rats of the ChABC group 2- GAP-43 and NF-200 expressions were significantly increased. Elevated expression of GAP-43 and NF-200 indicates that PGS/ChABC promotes healing by triggering even greater augmentation of axon growth and neuron sprouting	Combined treatment with PGS and ChABC resulted in the highest BBB scores, implying that PGS/ChABC further improved the recovery of motor function.

Abbreviations: N.S: Not specified; BDA: Biotinylated dextran amine; SCEP: Spinal cord evoked potential; MEP: Motor evoked potential; CTB: Cholera toxin B subunit; ChABC: Chondroitinase ABC; CSPG: Chondroitin sulfate prostaglandins; NPCs: Neural stem/progenitor cells; GFs: Growth factors.

Note: Motor functions assessed by the Basso, Beattie, and Bresnahan (BBB) scale.

covery after SCI (Jia et al., 2012). Likewise, edema is another essential component of the pathophysiology of SCI, which is initiated rapidly within minutes following injury (Rowland et al., 2008). Leonard et al. (2015) observed that deterioration of edema-induced injury was associated with more severe complications. Therefore, a systematic review of treatments targeting edema in SCI identified 3 main approaches to eliminate edema: inhibition of aquaporin 4 (AQP4), immunosuppression, and surgery. Furthermore, trifluoperazine, which prevents AQP4 localization, was proposed to be the most effective treatment, significantly reducing edema within a week after injection (Masterman & Ahmed, 2021).

Lemons et al.'s (1999) investigation is the first to report an increase in CSPGs at the injury site and in adjacent areas after SCI. Moreover, they showed that astrocytes are a source of CSPG, leading to a lack of neural regeneration. Besides, they suggested that exogenous ChABC administration could degrade CSPG, which indicates the role of CSPGs as inhibitory outgrowth factors. These findings also unveil a potential therapeutic effect of ChABC. Further studies have documented that local injection of ChABC is associated with protein-based neuronal regeneration (Barritt et al., 2006; Ishikawa et al., 2015). Moreover, Lee et al. (2010) found that ChABC administration affected CSPG and inflammation, reducing CSPG and GSK3β levels and accelerating neural growth (Yılmaz & Kaptanoğlu, 2015).

A systematic review and meta-analysis conducted by Yousefifard et al. (2022) demonstrated that ChABC has a moderate effect on locomotor function in animal models of SCI, with no differences in injury severity. They also revealed that the induction model of SCI and the number of ChABC injections did not influence the efficacy of ChABC on locomotor function in SCI. In mouse models, Carter et al. (2008) showed that ChABC was neuroprotective for cortical layer V projection neurons after ICV infusion. ChABC also prevented cell atrophy after localized delivery to the spinal cord, suggesting a possible retrograde neuroprotective effect mediated at the injury site.

Additional studies designed based on the combination of other treatment options like stem cells (Jevans et al., 2021), tissue engineering approaches (Raspa et al., 2021), sucrose (Raspa et al., 2019), photobiomodulation therapy (Janzadeh et al., 2020) antisense vimentin cDNA (Xia et al., 2015), poly(glycerol sebacate) (Pan et al., 2018), insulin + methylprednisolone (Yang et al., 2009) and rehabilitation (Ishikawa et al., 2015; Shinozaki et al., 2016; Wang et al., 2011) with ChABC showed improvement of the efficiency of Ch-ABC in SCI and improved functional outcomes. Additionally, a combination of ChABC and delayed injection of adeno-associated virus encoding the L1 cell adhesion molecule or pluripotent stem cell-derived NSCs in mouse models showed enhanced locomotor recovery after treatment (Lee et al., 2012; Suzuki et al., 2017). Furthermore, multiple injections of ChABC in Rhesus monkeys were associated with increased corticospinal axon growth, increased synapse formation by corticospinal terminals in the gray matter caudal to the lesion, and improved hand function (Rosenzweig et al., 2019). In this review, the functional outcomes assessed included motor, sensory, and autonomic functions, including forelimb and hindlimb function, gait, pellet-reaching task, fine-touch and mechanical hyperalgesia assessment, and residual urine volume assessment. Although the results were heterogeneous, most studies showed that ChABC administration improved functional outcomes in animal models.

This systematic review entails the histological aspects of the efficacy of intrathecal ChABC in SCI rats. Our comprehensive search identified 17 eligible studies assessing histopathological outcomes of intrathecal ChABC administration following SCI in rats. When analyzing treatment results by treatment phase, our results showed that ChABC treatment in the acute phase reduced necrosis and atrophic areas, increased tissue preservation, and increased sensory neuron plasticity and growth into and beyond the injury site. Moreover, ChABC increased the number of serotonergic fibers (5-HT), reduced neuronal apoptosis, increased the digestion of CSPG, promoted the differentiation of stem cells into neurons, and increased GAP-43, NG-2, chondroitin 4 sulfate, and BDA levels.

Regardless of the treatment phase, ChABC promoted the survival of serotonergic fibers, plasticity, and regrowth beyond the injury site, as well as rostral global plasticity and the survival of CST fibers. To the best of our knowledge, this is the first systematic review to evaluate the histopathological effects of intrathecal ChABC treatment. To make the results of the ChABC treatment more tangible, we compared them with studies using combined ChABC treatment. In a systematic review by Kwon et al. (2011b), the putative mechanisms underlying intraspinal ChABC injection for acute SCI were assessed. In this regard, axonal germination/growth of fibers, specifically serotonergic fibers, and the neuroprotective effect of intra-spinal ChABC, preventing neural atrophy, were the most promising mechanisms. Our results indicated that CST and serotonergic fibers sprouting, terminal arborization, and crossing were sig-

nificantly increased after ChABC treatment, similar to the results of ChABC treatment in combination with rehabilitation (Marsh et al., 2011), Nogo-A inhibitors (Zhao et al., 2013), and increased neurotrophin-3 levels (Massey et al., 2008). We also found that ascending fiber regeneration was significantly promoted after intrathecal ChABC administration. This finding was reproduced in 3 combinational treatment studies using neurotrophin-3, cell plant (Massey et al., 2008), and conditioning agents such as zymosan (Harel et al., 2012; Steinmetz et al., 2005). Grimpe et al. (2005) and Vavrek et al. (2007) reported that a combination of cell transplant and ChABC increased CST axon regeneration rostrally and promoted their elongation through the injury site and to the caudal sites. The articles we included in this area did not yield consistent results. While another study (García-Alías et al., 2008) reported increased regrowth length of CST axons into and beyond the injury site, the results of four other studies (Kim et al., 2006; Shinozaki et al., 2016; Wang et al., 2014; Yang et al., 2009) showed no significant effects on regrowth to caudal sites for ChABC treatment. It seems that when a substantial atrophic area is present after injury, a graft is necessary to provide a tissue scaffold for regenerating axons to traverse the injury site. Although it is well known that ChABC improves axonal sprouting and neural function by degrading CSPGs, the exact molecular mechanism underlying this process remains unclear. However, Hu et al. (2021) explored the key role of CSPGs in axon regeneration and neural apoptosis. They showed that the caspase activity is significantly increased within 2 to 11 weeks after injury. Importantly, ChABC reduces the total amount of functional caspase-3, validating the anti-apoptotic activity reported by Kwon et al. (2011b). Protein tyrosine phosphatase sigma is an example of a CSPG receptor involved in SCI-induced retrograde neural apoptosis. Correspondingly, the expression of PTPs, which was associated with neural apoptosis, decreased following ChABC treatment, demonstrating ChABC's anti-apoptotic activity in SCI. Regarding functional outcomes, we found that ChABC ssociated with better motor functions in animal models with SCI (García-Alías et al., 2011; Karimi-Abdolrezaee et al., 2010; Pan et al., 2018; Xia et al., 2015; Yang et al., 2009).

Conclusion

In summary, our systematic review of the available evidence for finding the histopathological effects of intrathecal ChABC administration in spinal cord injured rats suggests that this treatment can reduce necrosis and atrophic area and increase tissue preservation, increase sensory neuron plasticity and growth into and beyond the injury site, reduce the apoptosis of neurons, promotes the survival of serotonergic fibers, plasticity and regrowth to and beyond the injury site, the global plasticity and survival rostrally of CST fibers, increase digestion of the CSPG, differentiation of stem cells to neurons and the GAP-43, NG-2, chondroitin 4 sulfate, BDA level. ChABC treatment was associated with improved functional outcome in rats, mice, and primates. Although these findings are promising, further studies can provide additional evidence to support a final assessment of the risks and benefits of ChABC in SCI.

Strengths and limitations

As this is the first systematic review on the histopathological effects of ChABC treatment in SCI, results can be used to better understand the mechanisms underlying positive functional outcomes, understand the possible adverse effects to look for, and discover the pitfalls in studies that require more attention in future work. The most important limitation of this study is the small sample size in animal studies, which may both increase the risk of selection bias and render most effects non-significant. We grouped studies by intervention phase and injury model, and in some groups, there was only one study available, leaving very little evidence to deduct points. Furthermore, because studies using different enzyme administration regimens are limited, we did not summarize results by regimen. This limitation can affect the results and may be a source of the non-convergence.

However, clinical studies have higher priority and can more directly benefit individuals with SCI, whereas preclinical studies provide the fundamental basis for clinically approved treatments. Our study emphasizes the indispensable role of animal studies in advancing treatments for SCI and provides insight for bridging preclinical studies to patient care. This study also provided a comprehensive review of the histopathological effects of ChABC on rat SCI models. To gain a clearer understanding of ChABC's roles in SCI, we classified the reviewed studies by SCI phase, which is of high importance in this context.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran (Code: IR.TUMS.MEDICINE.REC.1398.886).

Data availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tool influenced the scientific content, data analysis, or conclusions of this work.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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