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Review Article

Cerebrolysin Use in Stroke and Spinal Cord Injury: Review of the Literature and Outcomes

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Abstract
Cerebrolysin (CBL) is a porcine brain-derived preparation with noticeable neurotrophic and neuroprotective activity. Treatment with CBL has significant potential to treat various debilitating neurological diseases such as traumatic brain injuries, ischemic stroke, and spinal cord injury. Although using CBL is not approved in the United States, about 50 countries have used it in clinics. CBL is a drug similar to neurotrophins with a multimodal action that effectively helps the central nervous system (CNS) and brain function properly through the protection, maintenance, and regeneration of the neural system. Furthermore, the safety and efficacy of CBL were approved following several clinical trials. Recent studies have shown its neurorecovery potential besides the neuroprotection ability. In addition, CBL efficacy has been reported in patients with moderate-to-severe strokes. A significant effect of CBL was observed in combination with neurorehabilitation versus neurorehabilitation alone. Following spinal cord injury (SCI), a cascade of neurochemical alteration happens in neural cells, including a reduction in producing neurotrophic and growth factors that lead to neural death. Previous studies indicated that exogenous compounds and supplements of different NTFs improve the spinal cord neuroprotection after injury. Among the existing drugs, CBL could be a valuable candidate, a compound mixture of various NTFs with multimodal action.
Keywords: Cerebrolysin, Neurotrophin, Stroke, Spinal cord injury, Treatment

Introduction

Cerebrolysin (CBL) is a drug composed of various low-molecular-weight neuropeptides and free amino acids, created through biotechnological processes. It contains different amino acids and neuropeptides such as brain-derived neurotrophic factor (BDNF), nerve growth factor, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor, orexin, enkephalins, and P21.[1,2]

CBL interestingly targets various pathophysiological mechanisms involved in both acute and chronic central nervous system disorders such as traumatic brain injury, dementia, stroke, and multiple sclerosis by promoting neuroprotection. Hence, its mechanisms improve neural survivor, neuroplasticity, and neurogenesis.[3] Specifically, CBL has neuroprotective effects by affecting numerous molecules as well as modulating various substrates, enzymes, and receptors implicated in glutamatergic, cholinergic, and γ-aminobutyric acid transmission. Following regulating caspase expression and other autophagic and apoptotic factors, it could induce neurogenesis and neurorestoration via neurotrophic factor and sonic hedgehog (Shh) signaling pathways activity.[4] CBL, as a multimodal drug, provides neurotrophic needs by mimicking the NTFs' activity. It protects cells from pro-apoptotic enzymes, oxidative stress, and excitotoxicity and also regulates inflammatory responses.[5]

Following the incidence of spinal cord injury (SCI), NTFs are necessary for spinal cord neurons to guide their development and growth and, importantly, reestablish their critical connections with target organs.[6] Thus, endogenous NTF deficiency at the lesion site of the spinal cord causes deformation in axons and progressive neuronal apoptosis.[7] Neurotrophin intervention for neurodegenerative disorders such as stroke has failed in clinical trials mainly because of poor blood-brain barrier permeability. New directions in scientific research and drug development for stroke, neurorehabilitation, and recovery were increasingly popular. As a result, NTFs are valuable factors in the treatment of stroke.[8] Therefore, the importance of drugs such as CBL as an exogenous NTF with the blood-brain barrier permeability is significant

for intervention in the early stage of neurodegenerative disorders. This review aimed to screen previous research investigating the therapeutic effects of CBL in SCI and stroke.

Pharmacology

CBL is a complex compound made from neuropeptides and amino acids that have been tested and used in several neurological conditions.[4] Therapeutic properties of CBL include neurogenesis, functional neuronal recovery or repair, and more effectively supporting nerve cell function. CBL activates the Shh signaling pathway and is responsible for organ development and organization. In the brain, CBL increased Shh and related receptors (Patched and Smoothened) via modulation of mRNA, which consequently promotes neurogenesis and oligodendrogenesis. Brain injury causes neural progenitor cells to differentiate into oligodendrocyte progenitor cells.[9] Neuroprotection was seen in spinal cord-injured animals when treated with CBL in a time- and dose-dependent manner. In vitro studies suggested that CBL also affects Schwann cell proliferation and elevates PNS regeneration/reconstruction.[1] Furthermore, neurogenic bladder dysfunction as a serious neurological disorder in the spinal cord could be a treatment target using CBL.[9]

CBL is a drug that mimics NTFs and has a multimodal role that effectively helps the central nervous system and brain to function accurately by protecting, maintaining, and regenerating the neural system.[9] CBL has been found to have structural fragments similar to NTFs such as glial cell line-derived neurotrophic factor, nerve growth factor, and BDNF, which stimulate neural progenitor cells for neurogenesis. CLB functions similarly to BDNF by stimulating the phosphatidylinositol 3-kinase/Akt pathway, which is critical in neural cell growth, differentiation process, and migration. Moreover, there is an interaction between the Shh signaling pathway and the phosphatidylinositol 3-kinase/Akt pathway to regulate cellular proliferation and neural precursors' regulation.[10,11]

CBL intervention helps reduce inflammatory response, pro-apoptotic enzymes, and free radical accumulation after neurodegenerative disorders. Furthermore, CBL moderates amyloid precursor protein expression, resulting in increased synaptic protein expression. It is also beneficial for neuroplasticity via neuronal network preservation, improving protein synthesis, and elevating synaptic density.[12]

PubMed and Google Scholar databases were searched to identify publications from peer-reviewed journals. We used Medical Subject Heading terms, including 'cerebrolysin', 'stroke', 'spinal cord injury', and 'therapy'. The search was conducted on May 1, 2023, and no search filters were used on publication type, language, or other fields in the expected periods. Then, reference lists of all relevant publications were manually selected to find advanced-qualified studies.

Cerebrolysin in Stroke

Previous studies reported that CBL increases neurogenesis and progresses functional outcomes following the stroke, and these findings encouraged researchers to investigate the clinical potential to improve this disorder.[13] Several clinical trials with over 1500 subjects have established the tolerability and safety of this drug and its clinical benefits in stroke patients.[14-17] Numerous studies reported the improvement effect of CBL on neurological outcomes in stroke patients in association with other physical, pharmaceutical, and speech therapies.[17]

Heiss et al[18] validated the safety and suitability of CBL in patients with acute ischemic stroke (AIS) while reporting no significant difference among groups. However, a significant decrease was observed in disability and mortality between severe stroke cases. In a study conducted by Muresanu et al[19] on the effect of CBL on recovery after stroke (CARS 1), it was found that CBL has a clinically positive effect on rehabilitating motor function after stroke. More precisely, patients in the intervention group experienced better upper-extremity motor function 72 hours after stroke than patients in the placebo group. Guekht et al[20] conducted a CARS 2 study with the same design but on a large scale. Interestingly, they did not support the previous CARS 1 study although CBL was tolerated in its sample. A randomized controlled trial demonstrated the beneficial effects of CBL on the improvement of neurological results and also its influence on the pulsatility index of the middle cerebral artery after acute focal ischemic stroke.[21] In the investigation on assessing the efficacy of CBL accompanied by early rehabilitation after stroke, Stan et al observed positive outcomes in the CBL-treated cohort. Overall neurological health of the patient who received CBL was improved, and a decrease in the impairment was reported in this group.[22] In another combination therapy with nootropics for the treatment of AIS patients, Tran et al demonstrated that CBL alone or in combination with other pharmaceutical agents is a safe and valuable therapeutic factor in both the acute and recovery stages.[23] Chang et al evaluated the combination of CBL and standardized rehabilitation therapy and revealed that in patients with severe motor impairment following the stroke, this therapeutic strategy has extra benefits compared to conventional rehabilitation therapy alone in motor function recovery.[24] Prior research by Chang et al reported a positive effect of CBL on cerebral tissue correlated to motor function, while no remarkable difference was observed among groups.[25] In addition, Lang et al[26] conducted a randomized controlled trial to evaluate the safety and efficacy of CBSL in combination with alteplase recombinant tissue-plasminogen activator. Modified rankin scale (mRS) as the primary study endpoint showed good outcomes (mRS 0 or 1) in 53% of patients on day 90 in both groups. The National Institutes of Health Stroke Scale (NIHSS) as the second outcome showed that in the CBL group, more patients had a significant improvement of 6 or more points after two,

five, 10, and 30 days. Notably, CBL had more beneficial effects compared to the effects seen with recombinant tissue-plasminogen activator alone.

A study by Gharagozli et al[14] evaluated the effectiveness, safety, and tolerability of CBL in the primary recovery phase following the AIS. They confirmed that CBL is safe, well tolerated, and effective in the early recovery phase after AIS. In addition, CBL showed a significant effect on the improvement of neurological and global function outcomes compared to placebo (Table 1).

Cerebrolysin in Spinal Cord Injury

SCI leads to the release of several neurochemicals and, consequently, the reduction of growth and NTFs from neural cells and tissues, resulting in cell exhaustion and finally causing neuronal death.[27] However, exogenous compounds and supplements of different NTFs improve the neuroprotection of the spinal cord after injury.[28]

Sahib et al[29] studied the impacts of CBL either, given alone or its titanium dioxide nanowired delivery on spinal cord-induced pathology, blood-spinal cord barrier instabilities, cell damage, edema formation, and evoked potentials in rats. They observed that nano-delivery of CBL using titanium dioxide nanowires when administered in low doses and before the injury can prevent spinal cord pathology at 5 hours, and if the drug was administrated immediately after SCI, it could have a profound effect, enhancing spinal cord evoked potential activity and neuroprotective ability. It also prevented the loss of a prominent negative peak and also increased its level further from pre-injury levels. Another study also reported that after chronic intoxication of engineered silver, copper, or aluminum (50–60 nm) nanoparticles, CBL led to a decrease in the exacerbation of neuropathic pain, spinal cord pathology, and blood-spinal cord barrier breakdown.[30]

Menon et al[31] examined the effect of intravenous iron oxide magnetic nanoparticles (10 nm in diameter and 0.25 or 0.50 mg/mL in 100 µL) in SCI animals and the therapeutic efficacy of CBL. The results showed that CBL therapy significantly reduces iron oxide magnetic nanoparticle-induced aggravation of SCI-induced cord pathology and improves neuroprotection. In the earlier study, they indicated that CBL also decreases plasma protein leakage,

Table 1. Stroke Studies Included in This Review and Main Outcomes

Disorder	Study	Intervention	Daily Dosage	Outcome	Reference
Stroke	Heiss et al	CBL	30 mL CBL daily or placebo (saline) intravenous infusion for 10 days + aspirin (100 mg daily)	NIHSS day 90: improved by 6 CBL / 5 placebo, CBL: 30 for both groups, mRS: 2 for both groups, global test MW = 0.50, and CI = 0.46	18
Stroke	Muresanu et al	CBL + SRP	CBL (30 mL/d) or a placebo (saline) once daily for 21 days, beginning at 24 to 72 hours after stroke onset + SRP for 21 days	ARAT day 90: an increase in 92.3% of patients in the CBL group/ 84.2% placebo, mRS: score of. 0–1 in 42.3% of patients in the CBL group/ 14.9% placebo	19
Stroke	Guekht et al	CBL	CBL (30 mL/d) or a placebo (saline)	No endpoints revealed significant improvement at 90 days for the CBL group, mild baseline levels of impairment revealed improvement after 90 days in the placebo group	20
Stroke	Amiri-Nikpour et al	CBL	30 mL CBL + for 10 days duration or normal saline + 100 mg ASA	NIHSS was significantly lower in the CBL group compared with the placebo group on day 60 and day 90, The median of PI in the right middle cerebral artery was significantly lower in the CBL group compared with the placebo group on days 30, 60, and 90	21
Stroke	Stan et al	CBL	30 mL/day CBL or to placebo for 10 consecutive days, started in the first 24–48 hours after stroke	NIHSS higher scores in the CBL group day 10: MW = 0.79, day 30: MW = 0.75, mRS day 30: Independent patients in the CBL group: 73.33% / placebo: 44.83%	22
Stroke	Tran et al	CBL + Nootropics	CBL (10 mL), other nootropics, or a combination of both	mRS: improvement in CBL 81.6%, combination 93.4% /placebo 43%, NIHSS: good responders CBL 77.5%, combination 92.5% / placebo 47.6%, MoCA scores CBL 23.3 ± 4.8, combination: 23.7 ± 4.1 /placebo 15.9 ± 7.7	23
Stroke	Chang et al	CBL + SRP	CBL or placebo with SRP for a 21-day treatment course	FMA-upper limb: T1–T2 significant improvement in the CBL group, MEP T1: positive response CBL 33.9% /placebo 27.5%, MEP T2: increased in both groups, CBL 42.4% /placebo 35.3%	24
Stroke	Chang et al	CBL	30 mL/d CBL or to placebo for 21 days	No significant difference was observed between the two groups, Total FMA: 42 CBL, 42.2 placebo, NIHSS: 8.4 CBL, 7 placebos	25
Stroke	Lang et al	CBL	CBL 30 mL/d for 10 days in combination with alteplase (rt-PA)	The combination of CBL with rt-PA is safe for the treatment of AIS but did not progress outcome at day 90. During the treatment period with CBL, more patients showed a favorable response to neurological outcome measures	26
Stroke	Gharagozli K	CBL	CBL 30 mL/7 days followed by 10 mL until day 30, or placebo once daily over four weeks	The effect size of NIH day 30: medium to large superiority of CBL compared to placebo (MW = 0.66; 95% CI; 0.55-0.78, $P = 0.005$). Effect sizes for the mRS (MW = 0.65; 95% CI; 0.54-0.76; $P = 0.010$) and the CGI (MW = 0.70; 95% CI; 0.55-0.85; $P = 0.006$).	14

Note. CBL: Cerebrolysin; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified ranking scale; MW: Mann-Whitney; CI: Confidence interval; SRP: Standardized rehabilitation program; ARAT: Action research arm test; ASA: Acetylsalicylic acid; PI: Pulsatility index; MoCA: Montreal cognitive assessment; FMA: Fugl–Meyer assessment; MEP: Motor evoked potential; rt-PA: Recombinant tissue-plasminogen activator; AIS: Acute ischemic stroke; CGI: Clinical global impression.

the water content of the spinal cord, and the overall number of damaged neurons. Additionally, they reported that high doses of CBL can be a valuable intervention in treating SCI subjects after nanoparticle intoxication.[3] In the study on the effect of CBL on motor-neuron-like NSC-34 cells, Keilhoff et al[32] suggested that CBL has a temporary anti-proliferative effect, has neuroprotective potency limited to the first 24 hours of oxygen-glucose deprivation, improves neurite reconstruction to a limited level, induces the expression of the calpain-1 protein, and influences calpain-mediated spectrin cleavage; however, CBL could not support regeneration or survival of motor neurons in organotypic slice cultures of the spinal cord. Moreover, intrathecal administration of IGF-I or CBL in adult rats with avulsion-induced cell death showed powerful effects of CBL on the survival of motoneurons.[33] In addition, our previous research on the influence of CBL on neurogenic bladder after SCI induction in adult rats showed that CBL exerts its function in a dose- and time-dependent manner. However, the infusion of 2.5 mL/kg CBL (4 weeks) resulted in an improvement in bladder compliance, and the bladder pressure pattern in the group receiving 2.5 mL/kg CBL exhibited a comparable pattern with the control group. Furthermore, the locomotion test showed a significant improvement ($P<0.001$) in the 2.5 and 5 mL/kg CBL-infused rats for four weeks,[9] as depicted in Table 2.

Conclusion

Animal model studies suggested that CBL has a noticeable impact on several different neurotrophic molecular pathways. Different molecular mechanisms and signaling pathways in both in vivo and in vitro studies showed that CBL has a high potential effect on neural regeneration, neuroprotection, neuroplasticity, and neural support and maintenance. In addition to the side effects of rapid injection, clinical trials reported that CBL is safe and well-tolerated in humans. In the current review, we highlighted basic research and clinical studies that proposed CBL treatment could have an improved effect on ischemic stroke patients and spinal cord-injured animals. In addition, studies suggested that CBL is effective for use in patients with stroke, and the administration time of the drug after the occurrence of stroke is an important issue. However, there is a controversial debate regarding the beneficial effect of CBL in enhancing recovery after neurological damage. Furthermore, studies suggested that the administration of CBL is effective when used in a critical time window and alongside the current traditional therapies. In addition, the literature review in SCI showed that the effectiveness of CBL is time and dose-dependent based on the type of spinal neuron injuries. However, some studies exhibited no significant beneficial effect of CBL following neurological damage.

Table 2. SCI Studies Included in This Review and Main Outcomes

Disorder	Study	Intervention	Daily Dosage	Outcome	Reference
SCI	Sahib et al	CBL, TiO2 nanowired delivery	CBL (5 mL/kg, i.v. 30 minutes before) alone or TiO2 nanowired delivery of CBL (NWCBL 2.5 mL/kg, i.v) delivered 2min after SCI	CBL and NWCBL increased SCEP activity and dissatisfied the development of cord pathology after SCI. NWCBL in low doses has higher neuroprotective effects on SCEP and cord pathology.	29
SCI	Sharma et al	CBL, Ag, Cu, and Al NPs	CBL (2.5 or 5 mL/kg, i.v) once daily after 2 weeks until the sacrifice of rats (4, 8m and 10 weeks), Ag, Cu, and Al NPs (50 mg/kg, i.p) once daily for 1 week	CBL with higher doses has neuroprotective effects in nerve-lesioned rats with NP intoxication.	30
SCI	Menon et al	CBL, IOMNPs	IOMNPs (10 nm in diameter, 0.25 or 0.50 mg/mL in 100 µL, i.v.), CBL (2.5 m L/kg, i.v.) either 30 minutes before IOMNP injection in the 4-hour SCI group or 4 hours after injury in the 24-hour survival groups	IOMNPs are safe for the CNS and CBL treatment prevented CNS pathology after a combination of trauma and IOMNP injection.	31
SCI	Menon et al	CBL, NPs from aluminum, silver, and copper (50-60 nm)	Engineered NPs (Al), (Ag), and (Cu) (50-60 nm) daily for 7 days (50 mg/kg, i.p.) in rats, CBL (2.5 and 5.0 mL/kg, i.v.) 30 minutes before SCI	CBL was highly effective in reducing the pathophysiology of SCI in both normal or NP-treated injured animals through strengthening BSCB function, most effectively in higher doses.	3
SCI	Keilhoff et al	CBL	CBL in dosage of 0.5 mg/m; (2.3 µL/mL), 2.5 mg/mL (11.6 µL/mL) or 5.0 mg/mL (23.2 µL/mL).	CBL has only isolated positive impacts on damaged spinal motor-neuron-like NSC-34 cells. High doses of CBL have adverse effects on the SCI treatment.	32
SCI	Haninec et al	CBL, IGF-I	IGF-I is prediluted in 1 mM acetic acid and then diluted in PBS for final concentration (360 µg/mL) after injury and 2 weeks after, and sacrificed in week 4.	Both IGF-I and CBL can reduce avulsion-induced loss of motoneurons in rats. No significant difference was observed between the effects of IGF-I and the CBL experimental model.	33
SCI	Abolhasanpour et al	CBL	CBL (1, 2.5, and 5 mL/kg CBL (4 weeks)	Improvement in the function of neurogenic bladder in 2.5 mL/kg CBL, and significant improvement in locomotor function in the groups received 2.5 and 5 mL/kg CBL for 4 weeks.	9

Note. SCI: Spinal cord injury; CBL: Cerebrolysin; TiO2: Titanium dioxide; i.v: Intravenously; i.p: Intraperitoneal; NP: Nanoparticle; SCEP: Spinal cord evoked potentials; IOMNPs: Iron oxide magnetic nanoparticles; AL: Aluminum; AG: Silver; CU: Copper; BSCB: Blood-spinal cord barrier; IGF-I: Insulin-like growth factor-I; PBS: Phosphate-buffered saline.

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The authors have no conflict of interest to declare.

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