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Spinal Cord Injury Repair Using Flash Graphene Based Treatments: A Literature Review

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Abstract

Introduction: Spinal cord injury is a prominent neurological complication and is characterized by motor, sensory and autonomic dysfunction. It can cause paralysis depending on the area that is affected within the spinal cord. There have been many attempts to mitigate this condition and regeneration of neurons is one of the leading cures.

Graphene is a carbon compound that is made from graphite. This unique one-atom layer is a versatile substance with potential uses in electronics due to its flexibility, conductance properties, and transparency. In the past, the creation of graphene was very expensive but now with the new technology of flash graphene, a method where carbon compounds are zapped into graphene flakes through flash heating, graphene is an accessible material for scaffolds to renew neurogenesis within spinal cord injury patients.

Methods: A literature search was conducted using predetermined inclusion criteria and resulted in multiple primary research papers that presented research on graphene as a potential scaffolding agent for spinal cord injury.

Results: Graphene based interfaces used within spinal cord injury have shown an increase in cell viability and neuron regeneration. These graphene interfaces do not create a disturbance in the electrical conductances that occur within the neuronal network. Graphene woven technology can also detect subtle muscle, which allows for quantifiable regeneration data.

Discussion: With the creation of graphene, the carbon becomes fixed in a solid state and can be used as a conductor within electronics. Graphene usage within the body is not considered toxic as long as it is used within measured concentrations. This technology can be used to significantly impact how patients with spinal cord injury recover, potentially regaining use of their previously paralyzed limbs through neuron regeneration on graphene interfaces such as scaffolds or nanoplatelets.

Keywords: spinal cord injury, graphene, flash graphene, nanoplatelets, cryogels, scaffolds, stem cells, environmentally friendly

Introduction

Graphene

Graphene is a hexagonal lattice sheet of carbon atoms covalently bonded in a single-atom layer that is typically considered two-dimensional (2D) [1], and is characterized by high mechanical strength, electrical conductivity, and optical transparency [2]. Andre Geim and Konstantin Novoselov discovered Graphene in 2004 and won a Nobel prize for their endeavors in 2010 [3]. Graphene exhibits a high tensile strength and a high Young's modulus which makes it a stiff and durable material suitable for the reinforcement of the mechanical properties of various materials and scaffolds [4]. These properties make graphene a suitable candidate for the previously mentioned cell-based therapies currently being developed to treat spinal cord injury; however, the compound is costly to manufacture on a large scale due the difficulty associated with its processing and production methods and the means to mass produce graphene yield various toxic byproducts [5]. Thus, as graphene shows promise in advancing technologies involved in spinal cord regeneration techniques, it would be meritable to investigate alternative forms of production such as flash graphene (FG) to mitigate the expenses and the waste that accompanies the production of the compound.

FG is a novel innovation from efforts to try to reduce single-use plastics in landfills. It is estimated that 70% of garbage is thrown into landfills, including many compostables [6]. The production of FG involves shredding the plastic, mixing it with black carbon, then applying Flash Joule Heating (FJH) in order to rearrange the carbon bonds in the plastic to the 2D lattice structure in graphene [1]. Other methods to manufacture graphene require harsh chemicals, an abundance of energy, sonication, or electrochemical methods which contribute negatively to the environment and are time consuming and costly, but FJH has a high yield with fewer environmental consequences

and energy expenditures [7]. The products of FJH have been verified via spectra analysis to have the same chemical properties as graphene derived from physical and chemical exfoliation methods [7]. Additionally, batch analysis has confirmed that there is a high consistency between batches [1,7]. One advantage of FG is that the layers are more than twice as dispersible via ultrasound sonication than graphene derived from other methods, making FG less time consuming to work with [7]. One drawback of FG is that FG tends to have a lower surface area than other graphene and a high variance in sheet size; thus, these are constraints which must be considered before utilizing FG [7]. FG demonstrates that there are graphene production methods that take less toll on the environment, and this review summarizes the use of graphene technology as a potential regenerative therapeutic in SCIs.

Spinal Cord Injury

Spinal Cord Injury (SCI) refers to any injury characterized by damage to any part of the cells and nerves within the spinal cord, ultimately leading to a number of motor, sensory, and autonomic impairments [8]. Furthermore, SCI is categorized into two types: complete and incomplete. The former involves a complete lack of motor and sensory function below the point of injury whereas the latter involves the maintenance of some motor and sensory function below the point of injury [9]. SCI is further categorized into primary and secondary injury: primary damage includes the immediate trauma to the spine which may induce fractures, dislocations, and ligament tears within the vertebrae while secondary damage is induced by primary injury and is characterized by the inflammation and damage to spinal tissues surrounding the site of injury [8]. Globally, approximately 250,000 to 500,000 individuals are affected by SCI annually and recovery from such an injury is rare as SCIs tend to cause lifelong disability and treatments are limited to mitigation of symptoms through surgery, rehabilitation, and pharmacological therapies [8]. However, research investigating stem cell therapy as a means of promoting spinal cord regeneration has shown promising therapeutic effects in enhancing the regenerative capacity of tissue within the spine [10]. One of the current limitations of this approach is facilitating a suitable environment for proper stem cell differentiation and axonal alignment; thus, studies have employed graphene as a material for creating nanoscaffolds for stem cell growth [11]. Graphene-based SCI repair technology is meritable to investigate as previous SCI treatments lack the possibility for long term care and many options lack accessibility.

Advancements in Using Graphene in Regenerative Medicine

Given graphene's unique 2D structure and the ease of adding functional groups to the carbon lattice structure, several researchers have investigated its implementation into regenerative medicine technologies [1]. Graphene can be used as a hydrogel, cryogel, powder, nanoplatelet, or film and can promote new neurons to grow and differentiate or deliver pharmaceuticals and nutrients to injured cells to promote healing [2,4,10,12]. Graphene oxide (GO) is graphene which has been functionalized, and is a commonly used form of graphene in biological systems as its electrophysiological properties allow for sustained cell signaling, without significant impact on function, and do not diminish cell survival, both of which are key factors in GO's biocompatibility [2,23]. Graphene cryogels are manufactured by combining collagen and graphene nanoscaffolds in order to create an optimal environment with elements from the natural extracellular matrix to encourage stem cell growth [12]. Graphene nanoplatelets (GnP) consist of multiple layers of graphene stacked upon each other, which stabilizes their electrical conductance properties [4].

Using FG in Regenerative Medicine

This review documents the current usages of graphene in spinal cord regeneration therapies and addresses the potential of FG to be used in the place of current commercially sourced graphene. We describe the research methods for deriving graphene in existing spinal cord regeneration literature, and we consider and speculate on protocols for modifying FG after its initial production, as there are no experiments employing FG in spinal cord regeneration. Utilizing FG could lower the cost, increase the quality of graphene, and decrease the environmental impact of research and subsequent therapies; thus, it is beneficial to consider the substitution [1,4,5,7].

Methods

An online search of the PubMed Database was conducted by entering keyword search terms 'graphene AND neuroscience', 'flash graphene', 'graphene AND spinal cord regeneration', 'spinal cord treatments', and 'flash graphene oxide'. Primary articles published between (2010 and 2023) which addressed the production of flash graphene or spinal cord regeneration therapies using graphene were selected. Additional primary papers were included in order to assess the current treatments for spinal cord regeneration. These papers were found using the PubMed database using search terms 'spinal cord regeneration therapies'. Only peer-reviewed articles published in English were considered.

Results

Non-Graphene Spinal Cord Regeneration Therapies

Though there has not been a treatment for spinal cord injury that has been proven to be 100% successful, there are several treatment options which have been employed or that are undergoing clinical trials [13]. The most common are as follows.

Lifestyle Changes

Increasing exercise after SCI has been shown to promote neuroprotection, regeneration, and rehabilitation by acting at the cellular level as well as at the whole organism level [13]. While being a non-invasive option, the efficacy of lifestyle modifications is limited in their capacity to alter biochemical interactions which prevent spinal cord healing after injury [14].

Stem Cell Therapies

Neonatal microglia, which may still have some stem cell properties, have been shown to promote scar-free healing after SCI, whereas adult microglia do not yield the same results [15].

Several studies in rodents have shown that Oligodendrocyte precursor cells (OPCs) and Schwann cells can improve functionality and motor control after traumatic SCI [15]. One private company has even obtained permission from the FDA to begin clinical trials in humans [16]. It is theorized that the OPCs help remyelinate neurons that survived the injury, as well as contribute to neurogenesis after SCI [17].

Stem cell therapies, though promising, have limitations including tumorigenesis and risk of rejection from the patient's immune system, thus there are several challenges that remain unsolved which prevent these therapies from being implemented clinically [18].

Hydrogels, Bioscaffolding and Exosomes

Among the more recent advances in SCI therapies is the use of hydrogels, exosomes, and bioscaffolds [19, 20, 21]. Hydrogels are unique in their ability to be injected to a specific injury site and their ability to carry neuroprotective biomolecules and scaffolding molecules which have the ability to scavenge molecules which cause damage to the injury site [19]. In 2022, one group used peptide amphiphile supramolecular polymers to enhance vascular growth, axonal generation, and ultimately survival of motor neurons after SCI [20]. Exosomes are being considered as a means of transporting neuroprotective biomolecules to the site of injury. They can be packaged effectively and delivered through the bloodstream, then ultrasound sonication is used to rupture the exosomes and deliver the biomolecules [21]. Several studies have focused on biomolecules that could promote healing after SCI, and one group found that a specific cocktail of growth factors including osteopontin, insulin-like growth factor-1, ciliary-derived neurotrophic factor, fibroblast growth factor-2, and epidermal growth factor, could promote axon regeneration after SCI [22]. Incorporating these growth factor cocktails into exosomes could be an effective delivery method.

Experimental Graphene-Based Spinal Cord Treatments

There are several existing forms of graphene that researchers have used to investigate spinal cord regeneration therapies, and primary articles on these graphene-based treatments are summarized in the following paragraphs and in Table 1. Though none of these therapies have been approved for clinical trials in humans yet, experiments using graphene-based materials in *vivo* rodents and various neurons in vitro have yielded promising preliminary results.

Graphene Oxide

GO reduces aggregation between graphene sheets and the functional groups serve as an insulator (arranged as shown in Figure 1) to prevent unwanted conductivity after being placed in biological systems. Graphene oxide is synthesized by oxidizing graphite into graphite oxide through manganese heptoxide and then exfoliated to create GO [23]. One study found that GO film was more biocompatible than a GO powder in promoting dopaminergic survival and differentiation [24], demonstrating the utility of GO films in promoting processes necessary for neural repair. Another study evaluated neuron and neuroglia responses to prolonged exposure to GO, specifically in spinal cultures [2]. Small GO nanosheets were synthesized by mixing sodium nitrate, sulfuric acid, potassium permanganate, and graphite flakes were oxidized and exfoliated through several rounds of centrifugation which separates pure GO from oxidation byproducts. Using mouse organotypic spinal cord 3D culture models, in vitro tissue was developed for 2 weeks in the presence of GO, and immunofluorescence and confocal microscopy were then used to quantify resident microglial response to GO exposure. Microglia potentially reduced synaptic activity as a result of GO accumulation despite a lack of inflammatory response or neuronal cell death. Another study implanted hydrogel GO nanoscaffolds into rats that underwent T2 hemi spinal cord transections [25]. The hydrogel GO nanoscaffolds were derived from sonicated GO dissolved in deionized water which was then centrifuged. To assess in *vivo* biocompatibility and measure the ingrowth of tissue components near the hydrogel, histological analysis was performed 3 months after spinal transection through staining and immunohistochemistry of spinal cord tissue.

Though GO technologies seem to promote necessary survival processes when implanted in neural tissues, one study went further, functionalizing graphene oxide with acetylcholine in order to test its viability in the CNS after injury to cholinergic systems [26]. The group tested their acetylcholine-functionalized hydrogels against graphene oxide hydrogels in vitro and observed more neural outgrowth with stable microtubule networks and larger cell bodies [26]. When the acetylcholine hydrogels were tested in *vivo* after injury in rats, there was a heightened astroglial response in the injured area, suggesting that the hydrogel facilitated healing [26]. Though this experiment was done in the CNS, the descending motor systems of the spinal cord also utilize acetylcholine, so the technique may also be effective in promoting outgrowth in spinal cord neurons

[26]. The group used UV absorption peaks to confirm that their functionalized graphene still demonstrated similar properties as graphene oxide, and a similar UV spectra comparison could be done with flash graphene derivatives to confirm the quality, purity, and properties of the flash graphene product [26].

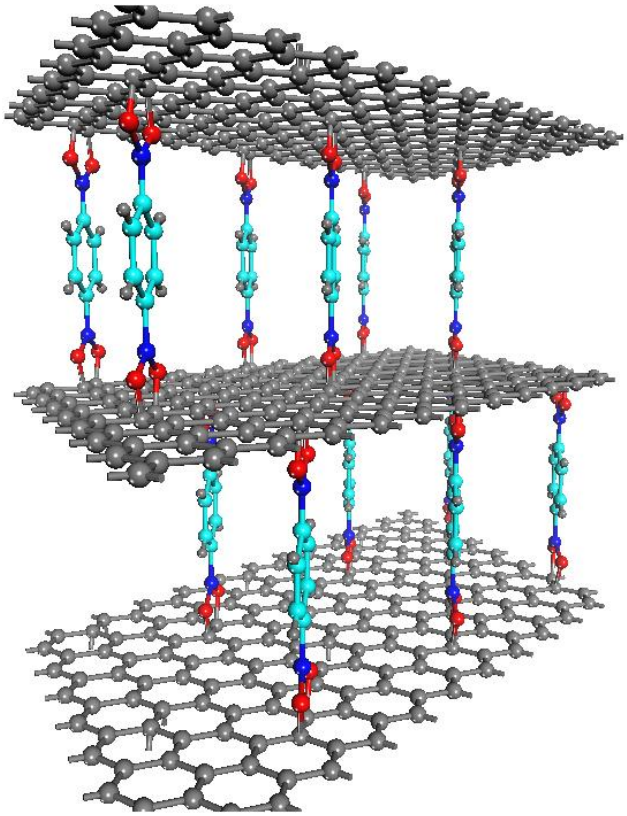

Figure 1. An image of the structure of graphite oxide. Exfoliation into a single layer produces graphene oxide. Image from the National Institute of Standards and Technology (public domain).

Graphene Monolayer Subtypes

Researchers have also investigated the effects of growing bone marrow derived mesenchymal stem cells (BM-MSCs) on graphene collagen cryogels [24]. This group used amino-functionalized graphene as a crosslinker for forming these collagen-based nerve conduits. Raman spectroscopy was performed to analyze the orderliness and crosslinking of collagen molecules in the developed cryogel, and the cryogels were exposed to electrical stimulation to test BM-MSCs stemness, neuronal differentiation, immunomodulatory response, and potential neuronal regeneration, all of which were shown to have been supported and proliferated. Human neural stem cells (hNSCs) have also been cultured on graphene-nanoparticle monolayers to evaluate axonal alignment and neuronal differentiation after exposure to growth factors [11]. These graphene-nanoparticle hybrid arrays were composed using positively charged silica nanoparticles and GO, and scanning electron microscopy and immunostaining detailed the enhanced differentiation of the hNSCs and aligned growth and extension of axons in the presence of GO. A standard cell viability assay assessed cell survival after 3 weeks of differentiation, finding that GO and graphene-silica nanoparticle hybrids enhanced cell survival after 3 weeks of differentiation as compared to the control.

Graphene Nanoplatelets

A common technique to create graphene nanoplatelets is a technique called ball milling. This includes taking graphite powder and combining it with chemicals that contain heteroatoms. This mixture is then put into a jar with high-speed rotating balls that use direct mechanical force to break down the carbon-carbon chemical bonds in the graphite and allow the heteroatoms to penetrate the compound and bond at the edges of the broken graphite. These nanoplatelets tend to be smaller in size than those created through chemical exfoliation. They are also more durable than graphene oxide structure because they tend to have fewer defects and higher conductances [27]. Another common method used to create GnP is liquid phase exfoliation. This technique uses ultrasound to sonicate large graphite molecules into graphene flakes. The ultrasound causes zigzag kinks to form along the graphite which then lead to cracks causing strips to fall off the compound. These strips are then chemically exfoliated to create flakes of graphene [28].

These nanoplatelets are molded into free standing films that can be used conducting research. Currently some of them are being used to create graphene-based interfaces that can interact with neurons and increase electrical conductances [29]. This can increase the neuron communication within the spinal cord leading to more functional usage. They can also be used to create scaffolds for the regeneration of a neuronal network [30]. Another study [29] found that these graphene-based interfaces do not create any distortion of electrical conductance signals allowing it to be a great potential new technology for possible neuronal repair.

Beyond Invasive Applications

Woven graphene has also been incorporated into wearable technology meant to detect subtle changes in muscle contractions [31]. A single layer of partially reduced graphene was sandwiched between two rubber layers made of polydimethylsiloxane capable of detecting muscle stretching. The technology is intended to monitor neuro-motordegenerative diseases and would be a useful tool in detecting advances in the healing process after implementing FG based regenerative therapies.

Table 1. Review of Regenerative Graphene-Based Primary Studies

Author Name	Type of Graphene Used	Sample Size	Method of Incorporation	Outcomes
Palejwala et al. 2016 [25]	Graphene Oxide (GO)	In *vivo*: 20 (19 male, 1 female) Wistar rats. 10 animals treated with GO scaffold and 10 animals treated with a hydrogel matrix as a control	GO nanoscaffold implanted on SCI lesion through hemi spinal cord transection	Biocompatibility of graphene for neuronal interfacing in *vivo*
Rodriguez-Losada et al. 2020 [24]	Graphene Oxide (GO)	Bulk cellular analysis	Culture cells were made to grow on GO substrates, in a film or powder form	GO promotes neural proliferation and differentiation
Pradhan et al. 2019 [26]	Graphene Oxide (GO), Choline-functionalized	In vitro: 96 well plates X 5,000 cells per well = 480,000 cells In *vivo*: mice divided into three groups (control, sham, and experimental) with five mice per group	Graphene-based hydrogel injected to injured mouse CNS in *vivo* and mouse neurons in vitro	No cytotoxicity observed, neurite branching increased near injection sites, and recovery enhanced in *vivo*. Neuronal cell markers and key microtubule outgrowths increased in vitro
Solanki et al. 2013 [11]	Graphene Oxide (GO)	Undisclosed	Made arrays of graphene-nanoparticle hybrid structures using positively charged silica nanoparticles and GO	Hybrid structures enhanced cell survival following periods of neuronal differentiation
Garcia-Cortadella et al. 2020 [29]	Graphene Nanoplatelets (GnP)	In vitro: plated (~ 30,000 cells) postnatal dissociated hippocampal neurons of mice on graphene-based substrate coverslips or control coverslips	Graphene based substrates were created through liquid phase exfoliation and ball milling techniques. Substrates were tested on brain cell cultures and had whole-cell patch clamp recording performed	Graphene based substrates are nonrestrictive interfaces, not altering neuronal signaling properties even without a cell adhesion layer
Moschetta et al. 2021 [30]	Graphene Nanoplatelets (GnP)	In vitro: n = 2, prepared from two independent samples of primary cortical cultures were used from 18-day old mice embryos. 10 random fields from each were chosen for sampling	Grew primary cortical neurons on polymer- based scaffold infused with various concentrations of graphene	Specimens were biocompatible, producing a mature neuronal network. Pure polymer platelets had low conductivity but incorporation of graphene restored electrophysiological parameters
He et al. 2022 [31]	Super-Compressible Graphene-	Undisclosed	Graphene oxide was mixed with ascorbic acid and heated to obtain a hydrogel, which	Wearable, time sensitive stretch sensors capable of detecting subtle muscle

Author Name	Type of Graphene Used	Sample Size	Method of Incorporation	Outcomes
	Based Cellular Material		was then shaped, degassed, and sandwiched between two layers of polydimethylsiloxane (a rubber used for lamination)	contractions
Agarwal et al. 2021 [12]	Collagen Graphene Cryogel	Undisclosed	BM-MSCs cells were seeded into fabricated collagen cryogels and then electrically stimulated	Cryogels facilitated increased collagen crosslinking, the proliferation of BM-MSCs, supported the stemness of BM-MSCs, increased immunomodulatory secretions, and supported neuronal differentiation of BM-MSCs

Discussion

Recently, there has been a significant expansion of work using graphene materials to develop treatments for spinal cord injury. However, a standard graphene type and manufacturing method has not emerged. Accordingly, it is necessary to discuss both the methods used to produce the graphene material used as well as what that type of graphene was able to accomplish in a specific study in order to properly assess the state of the field.

Graphene oxide has been shown to be biocompatible and even promotes cell differentiation and proliferation in neural stem cells [24, 25]. Graphene cryogels have been shown to encourage axonal alignment as well as enhanced differentiation [11]. Fluids which contain graphene nanoplatelets have been shown to effectively interface with neurons as well as create scaffolds which can facilitate neuronal growth [29, 30]. Graphene based substrates demonstrate unaltered baseline electrophysiological signaling. Graphene can also be used to create an advanced muscle contraction detection device which utilizes the flexibility and sensitivity of graphene in order to record subtle changes in muscle contractility. Combining these sensors with invasive graphene-based treatments could illuminate with precision the efficacy of the treatments. The conductive properties of graphene may provide the optimal conditions for spinal cord cells to proliferate and regain synaptic plasticity.

One of the main drawbacks to using graphene materials is the production costs and variability. However, using FJH, a flash graphene production method, could lower costs and save both time and energy for researchers, making graphene-based materials more convenient to investigate. The source materials of FG and the manufacturing procedure have a significantly lower environmental impact. FJH takes up less energy, which has both environmental and economic benefits [32]. Furthermore, FG is less expensive to manufacture than other forms [32]. Batch testing on FG has shown that FJH produces consistently high-quality graphene with the same properties of graphene of the same caliber produced from other methods; thus, utilizing FG would standardize the market's graphene price and graphene quality, as well as reducing landfill waste [32].

There are a few limitations to graphene-based spinal cord regeneration solutions. Even if spinal cord neurons could be encouraged to grow, it is necessary to ensure that they reach the correct destination and do not make incorrect connections. The biosafety of the use of graphene materials also needs to be further researched. There are some concerns within the scientific community that graphene could potentially be cytotoxic and cause oxidative stress, specifically through the use of graphene oxide [33]. The application of FG also has limitations and many questions to be answered. FG has not been studied in vitro and in *vivo* as extensively as graphene. While its properties are essentially the same as graphene, there are some concerns with the way it is produced and if that would be harmful within the human body. Through dose-dependent testing, research has produced that graphene nanoplatelets are non-cytotoxic if the amount of graphene used is within a certain threshold *in vivo* [34]. Based on a comparison of toxicity and harmful side effects, graphene, compared to graphene oxide, is a better material to be used with instruments that are created to mediate SCI.

Currently, there are multiple trials occurring in the preclinical stages and many scientists are hopeful that graphene-based materials will be brought into clinical trials within the next decade [35]. These animal models have shown promising results, as presented within this paper, and the switch into human clinical trials is hopefully not too

far away. Because this technology is so recent and the research being done with graphene materials is very new, there is a lack of sufficient evidence on the safety and efficacy of using graphene-based materials within human patients. There is much more research required to determine the safety of this material as well as its biocompatibility within the human body. The Food and Drug Administration (FDA) approval of drugs ranges from 10-12 years and for a new medical device is about 7 years after clinical trials have shown to be successful [36]. Furthermore, the costs of continuing research on preclinical models as well as developing it into technologically advanced gadgets will require substantial amounts of funding [36]. Therefore, it may be a while before the greater public sees graphene-based materials as a leading therapy for spinal cord injury but the current research shows some promising results [35].

Without the use of graphene, spinal cord regeneration treatments using oligodendrocyte progenitor cells have been shown to be effective in restoring function of the arms to quadriplegics who sustained spinal cord injury [37,15]. Perhaps the inclusion of graphene materials in the form of nanoplatelets, hydrogels, or cryogels could encourage the growth and differentiation of the oligodendrocyte progenitor cells and increase the efficacy of the treatments. Thus, graphene-based materials could be a catalyst to the progress of the neuro-regeneration field.

Conclusion

The results of this review suggest that the carbon lattice material, graphene, can be effectively incorporated into regeneration therapies after spinal cord injury. Graphene can be used in multiple forms, including cryogels, nanoplatelets, as well as wearable technology due to its electrical conductance properties. It has a minimal effect on toxicity *in vivo* and works to create an effective scaffold for the formation of a neuronal network. There are multiple methods to manufacture this graphene, but FG requires less energy production and produces less harmful waste than other methods. Additionally, the quality of FG is comparable, even superior, to other methods. Future directions for this research include determining if the FJH method impacts the properties of graphene within the body and whether FJH is economically sustainable. If FG emerges as superior after a rigorous and reproducible testing, discussion of further usage within the human body can ensue and FG would be a prime candidate for graphene-based materials used in spinal cord injury therapies.

Summary

Mehta, Enemuo, and Myers have prepared a literature review detailing the use of graphene-based materials for the treatment of spinal cord injuries. The report has a split focus on production methods for graphene, and the use of graphene oxide for spinal cord injuries.

List of Abbreviations Used

BM-MSCs: bone marrow derived mesenchymal stem cells
FG: flash graphene
FJH: flash joule heating
GO: graphene oxide
GnP: graphene nanoplatelets
OPC: oligodendrocyte precursor cell
SCI: spinal cord injury
hNSC: human neural stem cells

Conflict of Interest

The authors declare they have no conflict of interest.

Ethics Approval and/or Participant Consent

Because the study of this manuscript is taking the form of a literature review, there was no requirement for ethics consent or participant approval.

Authors Contributions

RSM: conceptualized and charted out the study, researched, acquired, and interpreted the data, drafted and revised the manuscript, and created the final manuscript to be published.
KE: conceptualized and charted out the study, researched, acquired, and interpreted the data, drafted and revised the manuscript, and created the final manuscript to be published.
SM: conceptualized and charted out the study, researched, acquired, and interpreted the data, drafted and revised the manuscript, and created the final manuscript to be published.

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References

[1] Luong DX, Bets KV, Algozeeb WA, Stanford MG, Kittrell C, Chen W, Salvatierra R, Ren M, McHugh E, Advincula P, Wang Z, Bhatt M, Guo H, Mancevski V, Shahsavari R, Yakobson B, Tour J. Gram-scale bottom-up flash graphene synthesis. Nature Publishing Group. 2020 Jan 1;577(7792):647–51. https://doi.org/10.1038/s41586-020-1938-0

[2] Musto M, Rauti R, Rodrigues AF, Bonechi E, Ballerini C, Kostarelos K, Ballerini L. 3D Organotypic Spinal Cultures: Exploring Neuron and Neuroglia Responses Upon Prolonged Exposure to Graphene Oxide. Frontiers in Systems Neuroscience. 2019 Jan 24;13. https://doi.org/10.3389/fnsys.2019.00001

[3] Gerstner E. Nobel Prize 2010: Andre Geim & Konstantin Novoselov. Nature Physics. 2010 Oct 5;6(11):836–6. https://doi.org/10.1038/nphys1836
[4] Chen Z, Narita A, Müllen K. Graphene Nanoribbons: On-Surface Synthesis and Integration into Electronic Devices. Advanced Materials. 2020 Sep 18;32(45):2001893. https://doi.org/10.1002/adma.202001893
[5] Safian MT, Umar K, Mohamad Ibrahim MN. Synthesis and scalability of graphene and its derivatives: A journey towards sustainable and commercial material. Journal of Cleaner Production. 2021 Oct;318:128603. https://doi.org/10.1016/j.jclepro.2021.128603
[6] Kaur P, Kaur GJ, Routray W, Rahimi J, Nair GR, Singh A. Recent advances in utilization of municipal solid waste for production of bioproducts: A bibliometric analysis. Case Studies in Chemical and Environmental Engineering. 2021 Dec;4:100164. https://doi.org/10.1016/j.cscee.2021.100164
[7] Wyss KM, De Kleine RD, Couvreur RL, Kiziltas A, Mielewski DF, Tour JM. Upcycling end-of-life vehicle waste plastic into flash graphene. Communications Engineering. 2022 May 26;1(1). https://doi.org/10.1038/s44172-022-00006-7
[8] Anjum A, Yazid MD, Fauzi Daud M, Idris J, Ng AMH, Selvi Naicker A, Ismail OHR, Kumar RKA, Lokananthan Y. Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. International Journal of Molecular Sciences. 2020 Oct 13;21(20):7533. https://doi.org/10.3390/ijms21207533
[9] Alizadeh A, Dyck SM, Karimi-Abdolrezaee S. Traumatic Spinal Cord Injury: An Overview of Pathophysiology, Models and Acute Injury Mechanisms. Frontiers in Neurology. 2019 Mar 22;10(282). https://doi.org/10.3389/fneur.2019.00282
[10] Liau LL, Looi QH, Chia WC, Subramaniam T, Ng MH, Law JX. Treatment of spinal cord injury with mesenchymal stem cells. Cell & Bioscience. 2020 Sep 22;10(1). https://doi.org/10.1186/s13578-020-00475-3
[11] Solanki A, Chueng STD, Yin PT, Kappera R, Chhowalla M, Lee KB. Axonal Alignment and Enhanced Neuronal Differentiation of Neural Stem Cells on Graphene-Nanoparticle Hybrid Structures. Advanced Materials. 2013 Jul 4;25(38):5477–82. https://doi.org/10.1002/adma.201302219
[12] Agarwal G, Kumar N, Srivastava A. Highly elastic, electroconductive, immunomodulatory graphene crosslinked collagen cryogel for spinal cord regeneration. Materials Science and Engineering: C. 2021 Jan;118:111518. https://doi.org/10.1016/j.msec.2020.111518
[13] Sandrow-Feinberg HR, Houlé JD. Exercise after spinal cord injury as an agent for neuroprotection, regeneration and rehabilitation. Brain Research. 2015 Sep;1619:12–21. https://doi.org/10.1016/j.brainres.2015.03.052
[14] Ahuja CS, Nori S, Tetreault L, Wilson J, Kwon B, Harrop J, Choi D, Fehlings M. Traumatic Spinal Cord Injury—Repair and Regeneration. Neurosurgery. 2017 Feb 21;80(3S):S9–22. https://doi.org/10.1093/neuros/nyw080
[15] Li Y, He X, Kawaguchi R, Zhang Y, Wang Q, Monavarfeshani A, Yang Z, Chen B, Shi Z, Meng H, Zhou S. Microglia-organized scar-free spinal cord repair in neonatal mice. Nature Publishing Group. 2020 Nov 1; 587(7835):613–8. https://doi.org/10.1038/s41586-020-2795-6
[16] Li N, Leung GKK. Oligodendrocyte Precursor Cells in Spinal Cord Injury: A Review and Update. BioMed Research International. 2015;2015:1–20. https://doi.org/10.1155/2015/235195
[17] Zhao Q, Zhu Y, Ren Y, Yin S, Yu L, Huang R, Song S, Hu X, Zhu R, Cheng L, Xie N. Neurogenesis potential of oligodendrocyte precursor cells from oligospheres and injured spinal cord. Frontiers in Cellular Neuroscience. 2022 Dec 22;16. https://doi.org/10.3389/fncel.2022.1049562
[18] Liu W, Ma Z, Li J, Kang X. Mesenchymal stem cell-derived exosomes: therapeutic opportunities and challenges for spinal cord injury. Stem Cell Research & Therapy. 2021 Feb 3;12(1). https://doi.org/10.1186/s13287-021-02153-8
[19] Shen H, Xu B, Yang C, Xue W, You Z, Wu X, Ma D, Shao D, Leong K, Dai J. A DAMP-scavenging, IL-10-releasing hydrogel promotes neural regeneration and motor function recovery after spinal cord injury. Biomaterials. 2022 Jan 1;280:121279. https://doi.org/10.1016/j.biomaterials.2021.121279
[20] Álvarez Z, Kolberg-Edelbrock AN, Sasselli IR, Ortega JA, Qiu R, Syrgiannis Z, Mirau P, Chen F, Chin SM, Weigand S, Kiskinis E, Stupp SI. Bioactive scaffolds with enhanced supramolecular motion promote recovery from spinal cord injury. Science. 2021 Nov 12;374(6569):848–56. https://doi.org/10.1126/science.abh3602
[21] Costăchescu B, Niculescu AG, Dabija MG, Teleanu RI, Grumezescu AM, Eva L. Novel Strategies for Spinal Cord Regeneration. International Journal of Molecular Sciences. 2022 Apr 20;23(9):4552. https://doi.org/10.3390/ijms23094552
[22] Anderson MA, O'Shea TM, Burda JE, Ao Y, Barlatey SL, Bernstein AM, Kim JH, James ND, Rogers A, Kato B, Wollenberg AL, Kawaguchi R, Coppola G, Wang C, Deming TJ, He Z, Courtine G, Sofroniew MV. Required growth facilitators propel axon regeneration across complete spinal cord injury. Nature Publishing Group. 2018 Aug 29;561(7723):396–400. https://doi.org/10.1038/s41586-018-0467-6
[23] Jiříčková A, Jankovský O, Sofer Z, Sedmidubský D. Synthesis and Applications of Graphene Oxide. Materials. 2022 Jan 25;15(3):920. https://doi.org/10.3390/ma15030920

[24] Noéla Rodríguez-Losada, Rune Wendelbob, Carmen del, Casares A, Guzmán R, Aguirre JA, Arraez MA, Gonzalez-Alegre P, Medina MA, Arenas E, Narvaez JA. Graphene Oxide and Reduced Derivatives, as Powder or Film Scaffolds, Differentially Promote Dopaminergic Neuron Differentiation and Survival. Frontiers in Neuroscience. 2020 Dec 21;14. https://doi.org/10.3389/fnins.2020.570409

[25] Palejwala A, Fridley J, Mata J, Samuel ErrolLG, Luerssen T, Perlaky L, Kent TA, Tour JM, Jea A. Biocompatibility of reduced graphene oxide nanoscaffolds following acute spinal cord injury in rats. Surgical Neurology International. 2016 7(1):75. https://doi.org/10.4103/2152-7806.188905

[26] Pradhan K, Das G, Khan J, Gupta V, Barman S, Anindyasundar Adak, Ghosh S. Neuro-Regenerative Choline-Functionalized Injectable Graphene Oxide Hydrogel Repairs Focal Brain Injury. ACS Chemical Neuroscience. 2018 Nov 14;10(3):1535–43. https://doi.org/10.1021/acschemneuro.8b00514

[27] Fan X, Chang DW, Chen X, Baek JB, Dai L. Functionalized graphene nanoplatelets from ball milling for energy applications. Current Opinion in Chemical Engineering. 2016 Feb;11:52–8. https://doi.org/10.1016/j.coche.2016.01.003

[28] Li Z, Young RJ, Backes C, Zhao W, Zhang X, Zhukov AA, Tillotson E, Conlan AP, Ding F, Haigh SJ, Novoselov KS, Coleman JN. Mechanisms of Liquid-Phase Exfoliation for the Production of Graphene. ACS Nano. 2020 Jun 29;14(9):10976–85. https://doi.org/10.1021/acsnano.0c03916

[29] Garcia-Cortadella R, Masvidal-Codina E, De la Cruz JM, Schäfer N, Schwesig G, Jeschke C, Martinez-Aguilar J, Sanchez-Vives MV, Villa R, Illa X, Sirota A, Guimerà A, Garrido JA. Distortion-Free Sensing of Neural Activity Using Graphene Transistors. Small. 2020 Mar 18;16(16):1906640. https://doi.org/10.1002/smll.201906640

[30] Moschetta M, Chiacchiaretta M, Cesca F, Roy I, Athanassia Athanassiou, Fabio Benfenati, Papadopoulou EL, Bramini M. Graphene Nanoplatelets Render Poly(3-Hydroxybutyrate) a Suitable Scaffold to Promote Neuronal Network Development. Frontiers in Neuroscience. 2021 Sep 20;15. https://doi.org/10.3389/fnins.2021.731198

[31] He Z, Qi Z, Liu H, Wang K, Roberts L, Liu JZ, Liu Y, Wang SJ, Cook MJ, Simon GP, Qiu L, Li D. Detecting subtle yet fast skeletal muscle contractions with ultrasoft and durable graphene-based cellular materials. 2021 Oct 5;9(4). https://doi.org/10.1093/nsr/nwab184

[32] Barbhuiya NH, Kumar A, Singh A, Chandel MK, Arnusch CJ, Tour JM, Singh SP. The Future of Flash Graphene for the Sustainable Management of Solid Waste. ACS Nano. 2021 Oct 11;15(10):15461–70. https://doi.org/10.1021/acsnano.1c07571

[33] Lammel T, Boisseaux P, Fernández-Cruz ML, Navas JM. Internalization and cytotoxicity of graphene oxide and carboxyl graphene nanoplatelets in the human hepatocellular carcinoma cell line Hep G2. Particle and Fibre Toxicology. 2013;10(1):27. https://doi.org/10.1186/1743-8977-10-27

[34] Salesa B, Tuñón-Molina A, Cano-Vicent A, Assis M, Juán Andrés, Ãngel Serrano-Aroca. Graphene Nanoplatelets: In *Vivo* and In Vitro Toxicity, Cell Proliferative Activity, and Cell Gene Expression. Applied sciences. 2022 Jan 12;12(2):720–0. https://doi.org/10.3390/app12020720

[35] Girão AF, Serrano M, António Completo, Paula A.A.P. Marques. Is Graphene Shortening the Path toward Spinal Cord Regeneration? ACS Nano. 2022 Aug 24;16(9):13430–67. https://doi.org/10.1021%2Facsnano.2c04756

[36] Van Norman GA. Drugs, Devices, and the FDA: Part 1. JACC: Basic to Translational Science. 2016 Apr;1(3):170–9. https://doi.org/10.1016/j.jacbts.2016.03.002

[37] Fessler RG, Ehsanian R, Liu CY, Steinberg GK, Jones L, Lebkowski JS, Wirth ED, McKenna SL. A phase 1/2a dose-escalation study of oligodendrocyte progenitor cells in individuals with subacute cervical spinal cord injury. Journal of Neurosurgery: Spine. 2022 Jul 1;1–9. https://doi.org/10.3171/2022.5.SPINE22167

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