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Mini Review

The Potential and Promising Application of Fullerenes in Pain Management and Anaesthesia

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Abstract

Fullerene, a carbon-based material, is being beneficially applied in nanotechnology on a limited but expanding basis. Some advantages of fullerene are its ability to react with nucleophiles and undergo various chemical reactions, such as reduction, oxidation, hydrogenation and halogenation. Some disadvantages of fullerene are its susceptibility to degrade in the presence of light and oxygen and decompose due to a shift from the excited singlet state to an energetically lower triplet state. Also, fullerene's hydrophobic and aggregate-forming characteristics are significantly challenging in its application in medicine. Nevertheless, fullerene has potential applications in managing neuropathic pain and anaesthesia. The stimulation of specific voltage-gated sodium channels results in pain disorders. Fullerene can block the channel pore, demonstrating fullerene's potential in managing neuropathic pain. In conjunction with nanorobot technology, fullerene might act as an anaesthetic or analgaesic agent and a nanomaterial for dental robots. Pristine C_{60} is relatively less toxic than other variants of nanocarbons, and in many instances, shows biocompatibility in humans. However, the manufacturing process of experimental-grade nanocarbon onion-like fullerene materials can be inconsistent (even within the same batch). Thus, performing reliable assessments and reproducible studies of their biological benefits, biocompatibility, and potential toxicity are problematic.

Keywords: *Allotrope; Anaesthesia; Analgaesic; Buckyball; Fullerene; Isoform hNa$_v$1.7*

Abbreviations

C_{60}: Carbon 60; CNT: Carbon Nanotube

Introduction

Carbon-based materials have constructive applications in nanotechnology. Fullerene has been of interest in medicine and research since its discovery [1-5], for which Kroto and colleagues were awarded the Nobel Prize in 1996 [6-10]. Fullerene is one of the numerous allotropes of carbon, such as diamond and graphite. The carbon atoms of fullerene are organized as a hollow sphere, tube, or ellipsoid. These carbon atoms are connected through hexagonal and pentagonal rings. Fullerene is named after Buckminster Fuller, who invented and popularized the allotrope's geodesic dome design [9,11,12].

Cylindrical carbon nanotubes (CNTs) or buckytubes and the spherical buckyballs are the well-recognized forms of fullerene [13-15]. A pure form of fullerene has the following characteristics: better close-packing than the impure form; lower solubility of bromo derivatives than fluorinated derivatives; lower density than carbon (3.51 g/cc vs. 1.65 g/cc); stability up to 1000°C; the ability to react with nucleophiles; and the capacity to undergo several chemical reactions, such as reduction, oxidation, hydrogenation, and halogenation [7,9,16]. Drawbacks of fullerene include its susceptibility to degrade in the presence of light and oxygen and to decompose due to a shift from the excited singlet state to an energetically lower triplet state [7,17]. Also, fullerene's hydrophobic and aggregate-forming characteristics are significantly challenging in its application in many fields, especially medicine [18-20].

Fullerene has applications in the following fields: medicines, textiles, packaging, toys, aircraft, transportation, and lubricants [13-15]. This study provides a review and summary of the applications of fullerene in pain management and anaesthesia.

Discussion

About 20% of the adult population encounters chronic pain that may result in work-loss and severe financial hardship. Thus, there is a constant search for substances that do not elicit the typical limiting factors and adverse effects of conventional analgaesics, such as dose-limiting side effects and addictive potential [21].

Fullerene's effect on voltage-gated sodium channels and pain management

Voltage-gated sodium channels are responsible for the propagation and amplification of signals in the neurons. Several studies have determined that stimulation of the voltage-gated sodium channel, isoform $hNa_v1.7$, results in pain disorders. Fullerene can bind $hNa_v1.7$ and block the channel pore, demonstrating fullerene's potential in managing neuropathic pain [22-24]. This $hNa_v1.7$-binding property of fullerene is a fundamental consideration regarding its potential use in pain control and anaesthesia.

No published and accessible research has directly assessed fullerene's use in anesthesia. However, considering the evidence that local anaesthetic agents, like lignocaine, act by blocking sodium channels and that fullerene can bind to $hNa_v1.7$ and block the same channels, by extension, there might be a role for fullerene as a local anaesthetic agent.

Fullerene's application in anaesthesia in dental science

Combined with nanorobot technology, nanoanaesthesia is used in dental treatment to induce unconsciousness. Fullerene can act as an anaesthetic or analgaesic agent and a nanomaterial for dental robots. In this procedure, a colloidal suspension of several active, analgaesic, micron-sized dental robots is introduced into the patient's gingiva. Once these robots contact the crown or mucosal surface, the nanorobots reach the pulp by passing through the gingiva sulcus, lamina propia, and dentinal tubules. This movement is driven by the chemical gradient and temperature variance, regulated by the dentist. On reaching the pulp, the robots desensitize (diminish) the nerve impulses in the tooth. Normal sensation is restored once the treatment is concluded, providing a needleless, anxiety-free experience for the patient. This type of anaesthesic is swift and reversible and has no adverse effects or complications [25-28].

Toxicity of fullerene materials in humans

The constraints in the application of fullerene include its toxicity, attributed to its crystal structure, surface modifications, and preparation methods. Typically, exposure toxicity is lower in samples with increased fullerene solubility [29]. Pristine C_{60} is relatively less toxic than other variants. In a large population of living organisms, the molecule did not demonstrate acute or sub-acute toxicity. Risk assessment programs evaluating its toxicity have been performed [30]. However, they were limited by low exposure and uncertainties regarding the quality of exposure and toxicity. Adequate data for chronic exposure and their endpoints, such as carcinogenicity, were not obtained in these studies. Thus, conclusions regarding exposure and toxicity of fullerene are unsettled. A decisive evaluation of the molecule's toxicity will require novel and innovative testing parameters [31-33].

The challenges of pure fullerene manufacture

According to Kerna and Flores (2020): "The outcomes of the manufacturing process of experimental-grade nanocarbon onion-like fullerene materials can be inconsistent (even within the same batch), making it challenging to perform reliable assessments and reproducible studies of their biological benefits, biocompatibility, and potential toxicity. Also, their dosage, timing, and duration should be further evaluated and established for therapeutic use in specific conditions" [34(p52)].

Conclusion

The unique structure of fullerene is primarily responsible for its extraordinary characteristics. One of the challenges of its application in medicine is its hydrophobic nature. However, conjugation of the molecule with other biological agents facilitates cellular penetration. Research on fullerene's possible applications in medicine is advancing. There have been breakthroughs and innovations. The role of fullerene in blocking sodium channel subtype $hNa_v1.7$ (which is implicated in chronic pain) has been established; local anaesthetic agents also act by blocking sodium channel, thus fullerene might also play role as a local anaesthetic agent and analgaesic. Still, further studies are needed to determine these functions of fullerene unequivocally. Data on the safety of fullerene are inconclusive, but most C_{60} toxicity studies found it to be safe *in vitro* (human and animal cell lines) and *in vivo* (in animals).

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Supplementary Note

This paper, as a mini-review, is designed as a brief introduction to nanocarbon onion-like fullerenes (NOLFs), regarding their application in pain management and anaesthesia. Other articles have been or will be published on the application of NOLFs in the cardiovascular system, gastrointestinal system, neurological system, respiratory system, veterinary medicine, agriculture, pharmacology and toxicology, and other topics. These distinct mini-review articles could have been combined into a much lengthier review or research article. However, to have done so, the subject matter would have resulted in only one publication in one journal to exclude other medical specialties. The purpose of these papers is to disseminate the purported biocompatibility and beneficial effects of NOLFs to the broadest audience of students, researchers, and medical practitioners as possible. The authors hope that the introduction to NOLFs' application in various and diverse disciplines spawns curiosity and further research regarding NOLFs and fullerene materials. Fullerene materials seem poised to become a vital part of the future of medicine, veterinary medicine, and agriculture. However, more research is needed to determine any adverse effects of their long-term use. Also, the NOLF manufacturing process requires standardization to provide consistent quality and batch samples. Dosage and duration of treatment with fullerene materials for specific conditions need to be established by evidence-based research.

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