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The evaluation of the biomedical effectiveness of poly(amido)amine dendrimers generation 4.0 as a drug and as drug carriers: A systematic review and meta-analysis

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ABSTRACT

The purpose of this study was to investigate the evaluation of the biomedical effectiveness of poly(amido)amine dendrimers generation 4.0 (PAMAM G4) as a drug and as drug carriers by a systematic review of literature and meta-analysis. The results obtained from meta-analysis concluded that drug therapy reduces the change of parameters in relation to the control. The impact of the drug administered to change the test parameters are dependent on the type of tissue. PAMAM G4 may be effective in vitro and in vivo as a drug and drug carriers and may have appropriate applications in various fields of medicine. PAMAM G4 dendrimers hold promises for nanomedicine.

1. Introduction

Dendrimers are hyperbranched, monodisperse, three-dimensional macromolecules with defined molecular weight and host–guest entrapment properties. They allow the precise control of size, shape and placement of functional groups and combine typical characteristics of small organic molecules and polymers that result in special physical and chemical properties. Poly(amido)amine (PAMAM) dendrimers represent a new class of polymers (Tomalia et al., 1985, 1986, 1990). They are also known as starburst dendrimers. The term 'starburst' is a trademark of the Dow Chemicals Company. As the chains growing from the core molecule become longer and more branched, generation 4.0 and higher dendrimers adopt a globular structure (Fig. 1).

The manufacturing process is a series of repetitive steps starting with a central initiator core. Classically, dendrimers are synthesized by sequential steps, by divergent (Tomalia et al., 1985) or convergent (Hawker et al., 1990) methods. In the divergent techniques, dendrimer grows outwards from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first generation dendrimer. The divergent approach is successful for the production of large quantities of dendrimers. The convergent methods were developed as a response to the weaknesses of the divergent synthesis. In the convergent approach, the dendrimer is constructed stepwise, starting from the end groups and progressing inwards.

2. PAMAM G4 as a drug

We performed a literature search in PubMed and Embase from April 2008 to April 2013. PubMed was the main search engine for primary research, supplemented by Embase and by direct consultation of specialty journals such as International Journal of Pharmaceutics, International Journal of Nanomedicine and Cell Biology International.

The dendrimer PAMAM G4 might be a useful as drug, for example, in diabetic rats. PAMAM dendrimers generation G 4.0 dendrimers reduce blood hyperglycaemia and restore impaired blood–brain barrier in streptozotocin diabetes in rats (Karolczak et al., 2012). Effect of PAMAM G 4.0 was assessed on heart and liver mitochondria in rats with diabetes (Labieniec et al., 2009). In this article, we assessed liver, myocardium and plasma in diabetic rats treated with PAMAM G4 by the use of a statistical scale.

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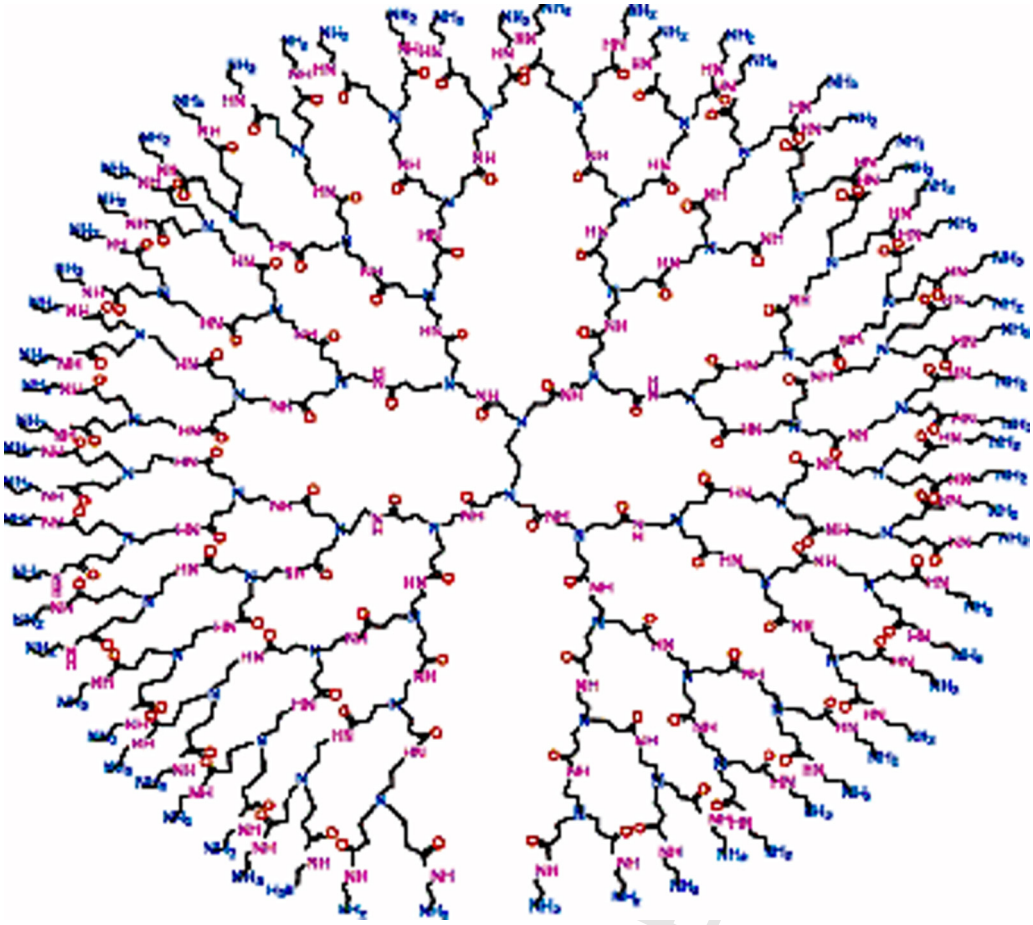

Fig. 1. Chemical structure of poly(amido)amine dendrimer (PAMAM) generation 4.0.

Biochemical parameters were considered creatinine, CoQ9, CoQ10, albumin, urea, total cholesterol, HbA1 and tocopherol.

3. PAMAM G4 as a drug carriers

An ideal drug carrier vehicle must be biochemically inert and non-toxic, while protecting the payload (drug) from dissociation until it reaches the target site. PAMAM G4 dendrimers as drug carriers were assessed for targeting nonsmall cell lung cancer (Liu et al., 2011a). A novel nonsmall cell lung cancer-targeting peptide (LCTP) and a fluorescence-labeled molecule (FITC) were conjugated to an acetylated polyamidoamine (PAMAM) G4 dendrimer to form a PAMAM–Ac–FITC–LCTP conjugate. The results showed that LCTP can effectively facilitate the targeting of PAMAM–Ac–FITC–LCTP to nonsmall cell lung cancer cells and tumors (Liu et al., 2011b). PAMAM G4 dendrimers as based contrast agents for MR (Zhu et al., 2008). PAMAM dendrimer generation 4-based gadolinium agents bG4-Gd and bG4-Gd-SA were tested in BT-474 tumor-bearing mice, as well as MCF-7 and BT-474 bilateral tumor-bearing mice in a three-step pretargeting approach. These agents can accumulate in the tumor tissues through the EPR effect (Zhu et al., 2008). PAMAM G4 dendrimers as anti-angiogenesis effect of PAMAM G4 dendrimers vascular endothelial growth factor antisesnse oligodeoxynucleotide on breast cancer in vitro (Gu et al., 2009). PAMAM G4 successfully transfected VEGFASODN into MDA-MB-231 cells and inhibited the expressions of the VEGF mRNA and protein (Gu et al., 2009). Polyamidoamine (PAMAM) dendrimers are one type of nano-vectors. The G4PAMAM/COX-2ASODN complex has antitumor properties on breast cancer in vitro and in vivo (Xin et al., 2012). PAMAM G4 is a promising gene vector with low cytotoxicity, high transfection efficiency and serum-resistant ability (Pan et al., 2011; Zeng et al., 2011). PAMAM G4 dendrimer derivatives conjugated with histidines and arginines may provide a promising polymeric gene carrier system (Yu et al., 2011). Liu et al. suggest that LA-PEG-b-PSD/PAMAM complexes exhibit selective targeting and cytotoxicity against HepG2 cells. In vivo antitumor studies showed that the LA-PEG-b-PSD/PAMAM/DOX complexes displayed higher antitumor efficacy compared with non-targeted PAMAM/DOX and DOX solution. These results indicate that this strategy should be applicable to the treatment of liver cancers (Liu et al., 2011a).

The comparative anti-inflammatory delivery potential of dexamethasone in an encapsulation-based and poly(amido)amine (PAMAM) dendrimer prodrug conjugation-based delivery systems (hydrophilic) was performed (Choksi et al., 2013). In vitro results suggest that the prodrug conjugates of PAMAM dendrimer deliver dexamethasone to be more efficient in comparison with liposome-based dexamethasone in terms of higher TNF-α inhibition. This study has implications in designing efficient prodrug nanocarrier systems for delivering dexamethasone (Choksi et al., 2013). Methylprednisolone was successfully conjugated to PAMAM-G4 dendrimer (Inapagolla et al., 2010). Conjugation of drugs to a dendrimer may provide an improved method for retaining drugs within the lung when treating such inflammatory disorders as asthma (Inapagolla et al., 2010). The study demonstrates that the physicochemical properties of PAMAM G4 influence skin transport. Findings can be used to design dendrimer-based nanocarriers for drug delivery to skin (Venuganti et al., 2011).