经鼻入脑纳米递药策略及其治疗脑部疾病研究进展

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摘要: 血脑屏障限制了大部分药物的脑部递送, 影响了中枢神经系统疾病的治疗。经鼻给药可通过嗅觉和三叉神经等通路让药物绕过血脑屏障直接到达脑部, 从而在减轻药物降解和避免肝首过效应的同时提高药物治疗效果。随着纳米技术的兴起, 将纳米制剂结合经鼻给药途径有望实现更好的脑靶向与脑部疾病治疗效果。本综述归纳了经鼻入脑各通路的特点, 总结了外泌体、液晶等近年来新型经鼻入脑纳米制剂的研究情况, 讨论了聚焦超声技术等提高入脑效率的新策略, 回顾了近年来经鼻入脑纳米制剂在治疗脑部疾病方面的研究, 分析了现阶段的研究困境并展望了其未来临床应用的前景。

关键词: 经鼻给药; 血脑屏障; 脑靶向; 纳米递药; 脑部疾病

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Advances in the strategies of nasal into brain nanodelivery and the treatment of brain diseases

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Abstract: The blood-brain barrier limits the brain delivery of most drugs and affects the treatment of central nervous system disorders. The transnasal drug delivery allows the drug to bypass the blood-brain barrier and reach the brain directly through pathways such as the olfactory and trigeminal nerves, thus improving the therapeutic efficacy of the drug while reducing drug degradation and avoiding hepatic first pass effect. With the rise of nanotechnology, the combination of nanoformulations with transnasal routes of administration is expected to achieve better brain targeting and treatment of brain diseases. On the basis of summarizing the characteristics of the various nose-to-brain pathways, this review summarizes the researches on novel transnasal nanopreparations such as exosomes and liquid crystals in recent years as well as new strategies to improve the efficiency of brain entry including focused ultrasound-mediated techniques. We also review the recent studies on transnasal brain entry nanopreparations in the treatment of various brain disorders and current research dilemmas, looking forward to the prospect of their future clinical applications.

Key words: intranasal administration; blood-brain barrier; brain targeting; nanoparticle delivery; brain disease

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近年来, 包括神经退行性疾病、脑血管疾病和神经精神疾病在内的脑部疾病发病率越来越高, 给社会和医疗系统带来了沉重负担[1,2]。血脑屏障 (blood-brain barrier, BBB) 是毛细血管网络和脑实质之间高度复杂的界面, 主要由脑毛细血管内皮细胞、星形胶质细胞、周细胞、相关神经元及其紧密连接组成[3], 是药物递送入脑的主要限制性因素[4,5]。BBB 可以选择性调控特定的营养物质 (葡萄糖、核苷、脂肪酸、氨基酸等) 从脉管系统进入脑实质, 限制有害的外源性生物分子 (如神经毒剂) 通过, 从而维持脑内稳态[6]。

经鼻给药可通过嗅神经和三叉神经等途径绕过血脑屏障, 将药物直接递送至中枢神经系统 (central nervous system, CNS) 实现脑靶向递送[7,8], 具有应用方便、无肝脏首过效应、可降低药物全身性不良反应等优势[9]。此外, 近期的一项鼻−脑通路相关研究提出将鼻−脑淋巴系统作为神经系统疾病的治疗新靶点[10]。传统制剂经鼻入脑存在渗透性差, 容易被黏膜纤毛清除等劣势, 而现代纳米制剂, 如聚合物纳米粒、脂质体、纳米胶束等, 可通过包载有效成分并在其表面修饰特定配体, 提高药物的稳定性, 增强鼻腔保留时间, 促进药物穿透鼻腔黏膜, 提高药物脑内浓度以实现对多种脑部疾病的治疗[11,12]。

近年来, 各种新型的纳米递药策略被用于提高药物经鼻入脑的效率, 在治疗脑部疾病, 如神经退行性疾病、神经胶质瘤等方面取得了巨大进步。本文将从经鼻给药的理论基础及瓶颈、代表性纳米制剂及提高其经鼻入脑效率的策略、经鼻入脑纳米递药策略在脑部疾病中的应用等方面, 对经鼻入脑纳米制剂近年来的研究进展进行综述, 以期为后续进一步深入研究提供参考。

1 经鼻入脑的理论基础

1.1 鼻腔生理学特征

人的鼻腔根据不同区域的解剖结构和功能, 分为前庭区、呼吸区和嗅觉区三部分。最外侧是前庭区域, 它被黏液层和负责黏液清除的纤毛所包围。呼吸区域负责呼吸功能, 覆盖了鼻腔的大部分, 约有 130 cm^2 的面积[13]。最内侧是嗅觉区, 它位于鼻腔的顶部, 与颅骨的筛骨相连, 位于筛板下方, 大约 10 cm^2, 仅占鼻腔总面积的 10%, 有大约 5 000 万个感觉感受器细胞, 是与 CNS 直接联系的部分[14]。该区域由基底细胞、微绒毛细胞、支持细胞和嗅觉上皮组成, 富含嗅觉神经元和一定的三叉神经神经元, 与大脑的嗅球直接相连[14]。因此, 鼻腔特殊的生理学构造决定了其与脑的密切联系, 具有脑部靶向的独特优势, 被广泛用于探索绕过 BBB 将药物直接递送至 CNS。

1.2 经鼻入脑途径

由鼻腔的生理学特性可知, 嗅觉区可作为将药物递送至 CNS 的主要区域。虽然经鼻入脑的确切通路和机制尚不完全清楚, 但有许多研究证据表明嗅觉通路和三叉神经通路的重要性[15], 是经鼻给药绕过 BBB 最主要和直接的途径。此外, 当药物进入鼻腔深处时, 也有部分通过呼吸区血管进入体循环, 穿过 BBB 到达脑部[16], 是经鼻入脑的次要和间接途径。其他经鼻入脑的途径主要包括鼻−脑淋巴通路等[17]。这些鼻−脑递送通路的研究均表明经鼻给药可普遍适用于直接向脑部递送药物, 且一些通路可以绕过 BBB, 如图 1 所示。

1.2.1 嗅觉通路 嗅觉通路由嗅上皮、固有层和嗅球组成, 是经鼻入脑最主要的通路。一方面药物与嗅神经元末端的纤毛嗅觉受体相互作用, 通过细胞内转运机制进一步向固有层和大脑移动, 到达固有层后, 药物沿着嗅鞘细胞形成的神经通道, 穿过筛板, 再穿过轴突和神经束, 到达嗅球和脑脊液 (cerebrospinal fluid, CSF)[18,19]。一旦药物转移到 CSF, 便会与间质液体混合并流动, 使药物能够分布到大脑中。另一方面药物到达嗅觉黏膜后, 也可通过支持细胞之间的紧密连接或嗅觉神经元和支持细胞之间的通道直接进入中枢, 使药物在 CNS、CSF 和嗅球中被吸收[20], 而嗅球可投射到大脑的不同区域, 如梨状皮质、杏仁核和下丘脑[21]。

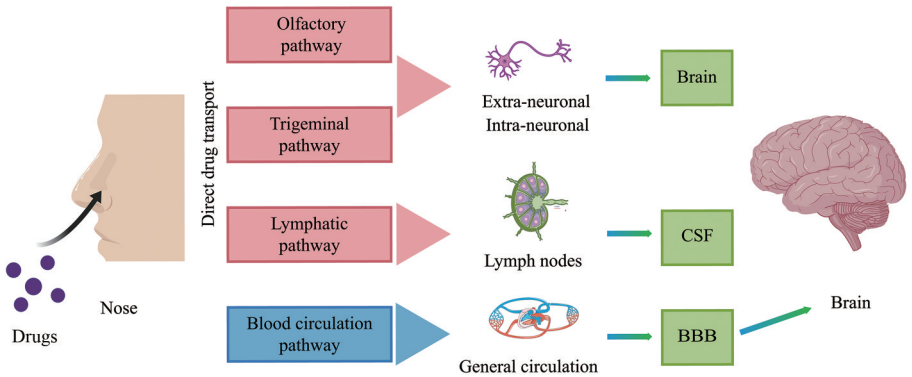

Figure 1 Different pathways of nose-to-brain transport

1.2.2　三叉神经通路　三叉神经是具有三个分支的第五对脑神经, 包括眼神经、上颌神经和下颌神经, 主要负责鼻腔的感觉[22]。三叉神经连接鼻腔和大脑, 使药物可以通过支配呼吸道黏膜的分支直接递送到脑干和大脑其他部位。其中眼神经和上颌神经支配鼻黏膜将药物由鼻腔递送到CNS[23]。这些分支由脑桥横跨脑干, 通过筛板进入前脑, 从而促进药物进入脑的尾部和前端[24,25]。此外, 这一途径通过轴突的细胞内运输和细胞外运输, 包括通过血管周围空间、神经周围通道的大量流动、扩散[26]。

1.2.3　淋巴通路　研究表明, 鼻腔淋巴系统与大脑保持着密切联系。CSF主要通过蛛网膜绒毛进入血液, 但还存在另一条途径, 这种途径将CSF从蛛网膜下腔排入筛骨筛板内的导管, 随后将CSF引导至鼻淋巴管, 最终排入颈部淋巴结[16]。此外, 嗅球周围的淋巴管形成了一个不间断的网络, 与鼻黏膜下层的淋巴管相连[27]。这些发现表明鼻腔淋巴通路与颅内CSF相连, 鼻腔给药可能利用淋巴通道引流, 使药物绕过血脑屏障进入脑间质, 为药物递送提供了潜在的途径。

1.2.4　体循环通路　体循环通路主要与呼吸区有关, 呼吸区黏膜有丰富的毛细血管, 血流丰富, 药物分子可通过黏膜吸收进入毛细血管然后进入血液循环[28]。此外, 也可通过嗅觉区的固有层进入血液循环。然而进入血液循环的药物必须通过BBB才能到达CNS, 这增加了药物达到治疗效果所需的时间, 并限制了递送至CNS的药物量。尽管如此, 这一过程对于低分子质量的亲脂性药物和具有高渗透性的药物是快速的[29], 到达体循环的少部分药物仍将穿透BBB (间接途径) 到达大脑。

1.3　经鼻入脑转运机制

药物及其纳米制剂经鼻入脑大部分沿着嗅神经或三叉神经发生。其基本过程是细胞转运, 分两种类型, 细胞内转运和细胞外转运。细胞内转运途径也称为药物转运的神经元内途径, 是一种有效的药物转运途径, 但其转运耗时长[30]。药物首先通过内吞作用从嗅觉和呼吸上皮细胞分别转运到嗅觉感觉神经元和外周三叉神经神经元, 然后将细胞内的内吞囊泡转运到神经元的投射位点, 最后通过胞吐作用释放。其中细胞内转运途径将药物从嗅神经输送到嗅球, 从三叉神经输送到脑干[31,32]。另一种机制为细胞外途径, 与细胞内途径相比, 能更快完成转运。具体分为两类, 一种是细胞旁路途径, 药物通过嗅上皮和呼吸道上皮细胞间的紧密连接分别到达嗅球和脑干; 另一种是跨细胞转运, 药物通过支持细胞受体介导的内吞作用或被动扩散递送到大脑各区[33,34]。以上经鼻给药的转运机制也为纳米制剂的设计与制备提供了理论基础。

1.4　经鼻入脑各通路特点

药物经鼻递送入脑的通路作用机制和递送效果不尽相同。例如, 嗅觉通路被认为是药物经鼻入脑最重要的途径, 是绕过BBB最直接的途径。通过嗅觉通路的细胞内转运, 药物最快可在约1～2 h内进入大脑, 而通过细胞外途径的药物则可在约半小时进入大脑[35,36]。三叉神经通路被证实可作为药物经鼻入脑的另一途径, 有文献报道[37]药物沿三叉神经传输的时间比嗅神经传输的时间长, 细胞内转运达到了17～56 h。鼻–脑淋巴通路不仅是药物经鼻入脑的途径之一, 还是神经功能障碍疾病中清除蛋白沉积物的重要通路[38]。体循环通路能让小分子质量的脂溶性药物通过毛细血管网络吸收进入全身循环, 然后进入脑部。然而这一过程必须穿过BBB才能到达CNS, 因此递送效率极为有限[29]。在药物经鼻入脑过程中, 可能一种途径占主导地位, 也可能多个途径协同发挥作用, 进而增加药物在脑中的蓄积, 这取决于药物的性质及其制剂的特性等。

2　经鼻入脑纳米制剂分类

经鼻给药可以绕过BBB将药物递送入脑, 这成为其最大优势。然而, 尽管存在诸多优势, 其缺点也较为明显, 例如相对较小的给药表面积, 导致其能入脑或者进入体循环的药物浓度受限[39]。目前, 经鼻入脑递药的关键瓶颈在于药物入脑效率较低, 其产生的原因主要包括药物的鼻黏膜渗透性差、黏膜纤毛清除、药物的酶促降解、药物在鼻腔保留时间短及生物利用度低等[40]。此外, 对于特定脑区的精准靶向也是面临的挑战之一[41]。而对经鼻入脑纳米制剂的研究则表明其具有多种优势, 例如能够保护封装的药物免受生物或化学降解[24], 通过表面修饰还可以减少黏膜纤毛清除, 增加药物嗅觉区域停留时间, 增强渗透性和生物利用度, 提高药物主动脑靶向能力[42]。一些特殊的纳米制剂 (外泌体) 和特定技术 (聚焦超声介导技术) 还能够实现对特定脑区的精准靶向[43,44]。经鼻入脑的纳米制剂, 包括聚合物纳米粒、聚合物胶束、脂质体等较为传统的纳米制剂; 新兴的仿生纳米制剂, 如外泌体等; 及液晶和无机纳米粒等。图2和表1[45-57]总结了近年来部分代表性经鼻入脑纳米制剂。

2.1　聚合物纳米制剂

聚合物纳米制剂是由聚合物组成的纳米系统, 主要包括聚合物纳米粒 (polymer nanoparticles, PN) 和聚合物胶束 (polymeric micelles, PM)。通过改变聚合物性质可以调整PN或PM的表面电荷、装载和释放药物的能力, 此外, 具有特定表面修饰的聚合物纳米制剂可

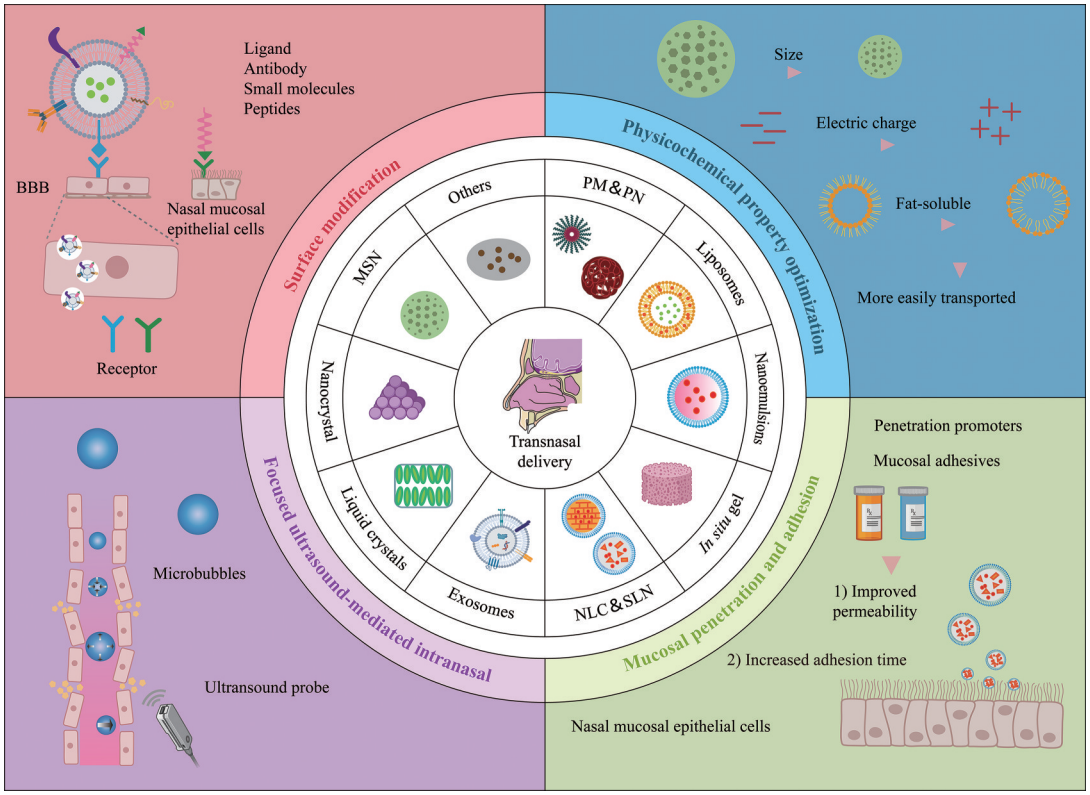

Figure 2 Classification of brain-targeting nanoformulations for transnasal delivery and strategies to improve brain entry efficiency. PM&PN: Polymeric micelles & polymer nanoparticles; NLC&SLN: Nanostructured lipid carrier & solid lipid nanoparticles; MSN: Mesoporous silica nanoparticles

以避免被免疫系统识别, 可到达并附着到特定的治疗靶点[58]。相较于其他纳米制剂, 聚合物纳米制剂制备简单, 易于表面修饰, PM可以通过自组装完成载药, 极大地提高了其应用的可行性, 广泛应用于目前经鼻入脑纳米制剂的临床前研究。

PN是由天然或人造聚合物组成的紧凑胶体系统, 在纳米尺度内具有高度可变的尺寸范围[59]。药物被溶解、包裹或附着在聚合物基质中[60]。其优点包括表面疏水性、高载药量及较强的控释能力等。同时将黏附性聚合物整合到PN配方中预计会导致更长的鼻黏膜停留时间[46], 以增强药物向大脑的递送, 提高药物的入脑效率。

PM与PN的不同之处在于它是由两亲性嵌段共聚物自组装而成, 形成疏水核心和亲水外壳[47]。其疏水性内核可包载疏水性或难溶性药物, 提高药物的稳定性, 而亲水性片段将成为疏水核心和外部水环境之间的稳定界面, 使其成为具有高动力学稳定性的纳米系统[48]。此外, 外部亲水性部分易于进行功能化修饰, 达到主动靶向和环境响应等效果。PM还能在鼻黏膜停留更长时间并减少黏膜纤毛清除, 从而提高药物经鼻入脑的效率[61]。

2.2 脂质体

脂质体 (liposomes) 是由磷脂和胆固醇双层构成的生物相容性囊泡[62]。其中有一个或多个隔室, 这取决于它们有多少双分子层。脂质体可以分别将亲水性和亲脂性化合物装载在内水相和脂质双层中, 被广泛用作多种药物共递送的载体系统。因为脂质体由磷脂和胆固醇组成, 而它们是生物膜的主要组成部分, 所以具有高度生物相容性和安全性 (无毒和非免疫原性), 并且还可以完全生物降解[49]。同时脂质体已经发展出几种变体, 其中之一是传递体。传递体是胶体囊泡的分散体, 主要由非离子表面活性物质组成, 如边缘活化剂和磷脂, 这些边缘活化剂通常是单链表面活性剂, 会破坏磷脂双分子层之间的连接, 使囊泡具备高度的灵活性和变形能力, 增强了它们的鼻黏膜渗透性, 进而提高药物经鼻入脑效率[63]。

2.3 脂质纳米粒

脂质纳米粒 (lipid nanoparticles, LNP) 一般指基于4种脂质成分: 可电离脂质、胆固醇、辅助脂质和聚乙二醇脂质构建的脂质递送载体[64]。包括两种类型, 一种是固体脂质纳米粒 (solid lipid nanoparticles, SLN), 其脂质基质由具有高度组织化的内部结构单一的固体

Table 1　Summary of brain-targeting nanoformulations for nasal administration

Nanocarrier	Preparation method	Structure	Feature	Ref.
Polymer nanoparticles	Emulsification-diffusion, solvent emulsion evaporation and nanoprecipitation	Compact colloidal system composed of polymers	Reduced mucociliary clearance, increased residence time, conjugated with ligands for targeted delivery	[45,46]
Polymeric micelles	Self-assembled, solvent evaporation	Self-assembled from an amphiphilic block copolymer comprising a hydrophobic core and a hydrophilic corona	Self assembly to manufacture, high hydrophobic drug loading, small size, easy surface modification	[47,48]
Liposomes	Ammonium sulfate gradient, thin film hydration	Bilayer vesicles composed of phospholipids and other lipid excipients	Co-loading of hydrophilic and hydrophobic drugs, prevented enzymatic degradation and mild toxicity	[49]
Nanoemulsions	High pressure homogenization, phacoemulsification	Heterogeneous system consisting of oil and water phases, stabilized by emulsifiers	Facilitated the encapsulation of lipophilic drugs, strong adhesion	[50]
In situ gel	Polymer desolvation, the film casting	Consisted of a solution that turns into a gel after stimulation	Drug release responsive to stimuli and pH, prolonged residency in the nasal cavity	[51]
Solid lipid nanoparticles	Solvent emulsion evaporation, thin film ultrasonic dispersion	Contained a lipophilic core composed of one solid lipid	Non toxic to nasal mucosa, controlled release properties, delivered peptides and macromolecular drugs	[52]
Nanostructured lipid carrier	High pressure homogenization, solvent emulsion evaporation	Contained a lipophilic core formed by a mixture of one solid lipid (in bigger quantity) with one liquid lipid	High encapsulation efficiency, improved drug stability	[53]
Exosomes	Ultracentrifugation	Cell-derived nanovesicles	Cellular origin, low immunogenicity, delivered to specific recipient cells	[54]
Liquid crystals	Spontaneously form	Lamellar, cubic, hexagonal crystalline mesophases	Thermodynamically stable, extremely large surface areas, incorporated numerous drugs	[55]
Nanocrystals	Media milling and high-pressure homogenization	Drug particles surrounded by a layer of the stabilizing agent	High drug loading capacity, delivered hydrophobic actives, used solvent-free and easily scalable techniques.	[56]
Mesoporous silica nanoparticles	Sol gel method, hydrothermal reaction	Honeycomb-like porous structure	Highly porous, density and total surface area being highly tunable	[57]

脂质组成; 另一种是纳米脂质载体 (nanostructured lipid carrier, NLC), 其内部脂质基质由固体和液体脂质的混合物形成。与脂质体和其他纳米制剂相比, 除了具备良好的生物安全性, LNP能够提供更高的疏水性药物包封效率, 其中NLC可以提供更高的载药量及更好的储存稳定性, 在疏水性药物经鼻递送入脑的应用方面有着显著优势[65]。

SLN与水包油乳剂的不同之处在于, 脂质在室温下是固体, 制备方法是先熔化脂质, 然后通过某种形式减小尺寸, 再用表面活性剂将所得颗粒在水相中稳定分散[66]。相关研究证明其能提高药物稳定性, 具备良好的生物相容性、耐受性及高载药量等优势, 同时由于脂质成分有利于黏附到嗅觉上皮, 可以增加制剂的鼻腔保留时间, 进而提高药物的经鼻入脑效率[67]。

NLC是由固态和液态脂质混合而成的脂质纳米颗粒, 它形成了一种无序的晶体基质, 与固态基质相比, 这种基质能更好地容纳疏水性药物, 允许更高的包封率和在储存过程中包封物的低释放[53]。同时这种纳米系统由生物相容和可生物降解脂质成分组成, 因此比其他一些纳米系统具有优势。此外, NLC可防止药物的酶降解, 增加在药物鼻腔的保留时间, 减少黏膜纤毛清除, 进而提高药物的经鼻入脑效率。其经鼻腔给药也已被证明可将药物输送到脑。

2.4　纳米乳

纳米乳 (nanoemulsions, NE) 是由两个不相容的相 (水和油) 组成, 由一个或两个乳化剂稳定的亲脂体系[68]。主要包括油包水 (W/O) 和水包油 (O/W) 两种类型。亲脂性药物可以溶解在油相中, 当药物从油相释放到鼻腔时, 可以形成纳米沉淀物, 这种沉淀物具有很高的比表面积, 可以提供快速的溶解速度[69]。此外, 在NE中添加黏膜黏附剂可以克服黏膜纤毛清除, 进一步延长药物在鼻腔吸收部位的停留时间, 从而提高生物利用度。良好的亲脂性和鼻黏膜渗透性及其对药物的增溶效果使它们也常被用于提高药物经鼻入脑效率。相较于其他一些纳米制剂, 纳米乳的增溶能力较强, 常用于提高一些难溶性药物的溶解性。

2.5　原位凝胶

原位凝胶 (*in situ* gel, ISG) 是由聚合物溶液或低黏度液体组成, 能在用药部位发生相转化, 由液态转化为半固体凝胶状态的新剂型[51]。ISG在用药部位响应生理环境 (如pH值、温度等) 的变化而表现出溶胶–凝胶转变。它们对刺激的反应类型可分为两大类: 物理

交联 (温度、超声波、光、机械应力) 或化学交联 (pH 和离子强度)。此外, 基于脂质的纳米制剂被加入 ISG 中, 提供了脂质基质和水凝胶网络的双重保护, 可以实现更长效的药物递送[70]。这些制剂以溶液的形式给药, 一旦进入鼻腔, 由于 pH 或温度等刺激引起聚合物构象的变化而形成水凝胶, 具有较强的缓释作用, 可以显著改善药物在鼻腔中的保留时间, 增强药物经鼻入脑效率, 常应用于一些需要持续释放以产生药效作用的药物。因此, ISG 在经鼻入脑递送治疗药物方面有较好的应用前景。

2.6 外泌体

仿生纳米递送系统 (biomimetic nanodelivery systems, BNDSs) 一般指由生物体或微生物中提取和纯化的内源性物质, 例如细胞膜、细菌、病毒和外泌体等构建的药物递送系统[71,72]。与传统纳米制剂相比, BNDSs 具有高度生物相容性和低免疫原性。此外, 某些细胞膜倾向于定位到特定组织或肿瘤, 可以利用细胞膜的表面蛋白和携带的生物活性分子实现药物的精准递送, 从而对特定疾病发挥高效的多重靶向作用[43]。其中通过经鼻给药递送方式的 BNDSs 通常为外泌体 (exosomes, EXO)。

外泌体是约 30～150 nm 的细胞衍生纳米囊泡, 几乎所有类型的细胞都会主动分泌, 并且在生物体液和中枢神经系统组织中含量丰富, 其疏水性和低水溶性使它们能够跨越 BBB, 同时因其细胞间通讯介质的作用和高安全性、无免疫原性等特点, 目前被主要用作蛋白质、miRNA 的载体[54]。此外, 有研究表明外泌体具有通过小胶质细胞吸收和跨细胞运输神经保护化学物质来降低大脑中 β-淀粉样蛋白水平的能力, 通过经鼻给药可有效地将脂肪间充质干细胞外泌体递送至大脑中的神经元和小胶质细胞[73,74]。由于这些特性, 将外泌体应用于经鼻入脑递药来提高入脑效率和精准靶向特定脑区已获得了广泛的关注和研究[75]。

2.7 晶体纳米制剂

晶体是微观物质单位 (原子、离子、分子等) 按一定规则有序排列的结构, 晶体纳米制剂则是由纳米级别的晶体组成的递药系统。常见的经鼻入脑晶体纳米制剂包括液晶 (liquid crystals, LC) 和纳米晶 (nanocrystals, NC)。

LC 由性质介于常规液体和固体晶体之间的物质组成, 是一种具备非晶液体流动性和固体晶体各向异性的物质中间态[76]。其中间相被认为是具备有序分子排列的胶束, 其特征是疏水性和亲水性区域交替, 通过增加表面活性剂的浓度, 可以产生层状、六方和立方液晶等独特的微观结构形式[55]。制剂中的液晶相具有热力学稳定性, 并且包含极大的表面积, 能结合多种药物而不受其溶解度的影响[77], 因此可将其应用于难溶药物的鼻–脑递送。有研究证明, 鼻内给予液晶制剂可增强亲脂性模型药物曲尼斯特向大脑的输送和大脑区域的分布, 其中基于 C_{17}-单甘油酯的液晶制剂具有高包封率, 能负载更多药物, 同时具有较高的黏性, 可以增强药物的鼻腔保留时间, 并表现出更高的将药物转运至大脑的能力[78]。

NC 可定义为由 100% 结晶态药物组成的亚微米颗粒 (< 1 μm)[79]。而当药物 NC 悬浮在一种或多种稳定剂的水溶液中及其他非水液体中, 该系统通常称为纳米悬浮液。同时为进一步延长与鼻黏膜接触时间的成功技术是包含 NC 的原位凝胶。与其他纳米递药系统相比, 因不含载体材料, 其载药能力可提高至约 100%, 具有长期稳定性、中性 pH 值, 广泛应用于递送疏水性活性物质[56]及不易生物降解的药物。鼻内递送的 NC 可以通过增加与鼻黏膜的接触面积, 提高药物在鼻腔的保留时间来增强药物吸收, 同时促进药物穿过黏膜屏障, 进而提高入脑效率[80]。

2.8 介孔二氧化硅纳米粒

介孔二氧化硅纳米粒 (mesoporous silica nanoparticles, MSN) 具有蜂窝状多孔结构, 有数百孔道 (介孔), 具有吸收分子的潜力。与传统纳米制剂不同, MSN 具有高表面积 (> 900 $m^2 \cdot g^{-1}$)、大孔体积 (> 0.9 $cm^3 \cdot g^{-1}$), 并且还具有在非常窄的尺寸分布 (一般 2～10 nm) 上可调孔径的额外优势[57]。同时还具有出色的物理化学稳定性和药物保护能力[81], 可以减少肽和蛋白质等在鼻–脑递送过程的降解[57], 提高药物的入脑效率。目前有研究将帕纳替尼负载于 MSN 中, 结果证明 MSN 组的帕纳替尼脑中浓度是游离组浓度的 8.9 倍, 经鼻入脑效率显著提高 [82]。

3 提高纳米制剂经鼻入脑效率的策略

3.1 表面修饰

对纳米制剂表面进行修饰改造是提高其经鼻入脑效率的重要方式。药物递送特性一般与表面涂层和生物系统的相互作用有关, 因此可以选择合适的配体对制剂进行表面改性以提高入脑效率。第一类是在嗅觉区域表达受体所对应的配体, 常见的如乳铁蛋白 (lactoferrin, Lf)[83]和其他一些糖蛋白[84]及麦胚凝集素 (wheat germ agglutinin, WGA)、橙黄网胞盘菌凝集素 (aleuria aurantia lectin, AAL) 等, 被证明可分别和乳铁蛋白受体 (LfR)、*N*-乙酰葡糖胺、岩藻糖残基等结合从而促进药物鼻–脑递送[85]。另一类通过促进各种生物活性分子细胞内运输, 提高对鼻黏膜的穿透, 进而提高经鼻入脑效率, 如细胞穿透肽 (cell-penetrating

peptides, CPP)[86]、HIV-1病毒转录调节蛋白片段 (trans-activator of transcription, Tat)[87]、狂犬病毒肽 (rabies virus glycoprotein, RVG)[88]及传统中药成分如冰片 (borneol, Bo)[89]。此外, 部分已经穿透鼻腔黏膜的制剂会进入体循环然后穿越BBB, 原理为脑毛细血管内皮细胞表达的受体与相应配体相互作用, 通过内吞作用促进小细胞形成, 形成的小细胞释放配体, 通过胞吐作用穿过血脑屏障进入CNS[90], 从而提高入脑效率, 包括转铁蛋白受体等。受体介导的内吞作用的有效性取决于受体的类型, 而不依赖于递送分子的大小, 为经鼻递送大分子药物提供了方向。表2[87,88,91-97]总结了一些重要的受体介导的经鼻给药纳米制剂或表面改性的纳米递药系统。

3.2　改变理化性质

纳米制剂理化性质的改变可以提高其经鼻入脑效率。纳米制剂的粒径是影响药物经鼻递送至大脑的最重要和关键的理化因素, 因为粒径越小, 制剂黏液渗透阻力越小[98], 尺寸范围为100～200 nm的纳米粒子可以很容易地通过嗅觉上皮细胞运输。鼻黏膜带负电荷, 由于静电相互作用, 阳离子纳米制剂容易被细胞内化[99]。此外, pH等理化参数也会影响纳米制剂的入脑效率。为保证药物的黏膜吸收, 鼻腔药物递送系统需尽量保证最多的药物处于非电离状态, 同时为防止鼻腔刺激、细菌生长和黏膜损伤, 制剂的理想pH值要求在4.60～6.50之间[100]。通过改变理化性质能在一定程度上提高纳米制剂的入脑效率。

3.3　使用渗透促进剂和黏膜黏附剂

提高纳米制剂的经鼻入脑效率可以从提高制剂生物膜的渗透性和制剂在鼻腔的停留时间两方面展开。渗透促进剂或吸收促进剂是最通用的功能性制剂成分, 可以促进制剂穿透黏液层、上皮细胞膜等, 进一步提高纳米制剂入脑效率[101]。常见的渗透促进剂包括表面活性剂、环糊精和阳离子聚合物等[102], 其在经鼻入脑纳米制剂的应用主要包括脂质和表面活性剂组成的SLN, 基于环糊精的纳米粒及阳离子聚合物纳米制剂。而黏膜黏附剂则能与黏液相互作用并增加制剂在鼻腔内的停留时间, 作用机制为聚合物黏附于细胞结合的黏蛋白, 延长在黏膜处的停留时间, 从而改善药物摄取[103]。常见的黏膜黏附剂包括壳聚糖、聚丙烯酸和卡波姆等[37], 常应用于壳聚糖纳米粒、聚丙烯酸修饰纳米粒和基于卡波姆的凝胶。虽然二者都能从不同方面提高纳米制剂的入脑效率, 但是一些渗透促进剂对鼻黏膜的刺激性和黏膜黏附剂的非特异性一定程度制约了二者的使用。

3.4　聚焦超声介导技术

聚焦超声介导的鼻内给药 (focused ultrasound-mediated intranasal, FUSIN) 是一种新型的脑部递药技术, 它利用经鼻给药途径的独特优势, 将聚焦超声 (focusedultrasound, FUS) 与微泡 (microbubbles, MBs, 一种超声造影剂) 相结合[104], 可以克服药物鼻内递送效率低, 不能专门针对患病的大脑区域等限制, 实现将治疗药物有效递送到特定的大脑区域[44]。FUS利用可以穿透头皮和颅骨的超声波诱导静脉注射的微泡扩张和收缩。由于微泡尺寸相对较大 (1～10 μm), 它们被限制在血管内, 从而推拉相邻的血管壁, 导致血管和周围组织的扩张和收缩, 产生“微泡泵效应”, 此效应可能会导致分布在BBB以外血管周围空间的经鼻给药的药物的渗透增强, 暂时增加BBB通透性[105]。已有研究显示该技术能局部增强经鼻给药抗程序化细胞死亡配体1 (programmed cell death 1 ligand 1, PD-L1) 抗体向大脑的输送能力, 用于脑胶质瘤治疗[106]。另一项研究显示FUSIN安全高效地将AAV5-EGFP递送至大脑目标空间位置, 包括浅表大脑部位 (皮层) 和深层大脑区域 (脑干)[44], 如图3所示。这些研究结果表明FUSIN是一种很有前途的脑部药物递送方式, 可以提高某些纳米制剂通过经鼻给药途径对不同脑区的递送效率。

4　经鼻入脑纳米递药策略在脑部疾病中的应用

由于鼻腔的特殊构造, 使其相较于其他给药途径

Table 2　Examples of surface modified nanoparticles for applications in intranasal delivery. HA: Hyaluronic acid; Tf: Transferrin

Surface modification	Carrier	Payload compound	Size/nm	Targeting effect	Ref.
Lf	LNPs	PTX/HePc	364 ± 5	C_{max} ↑ (2.33 times) $AUC_{(0-24)}$ ↑ (2.92 times)	[91]
Lf	NEs	HupA	16.74 ± 0.47	C_{max} ↑ (1.13 times) $AUC_{(0-t)}$ ↑ (1.98 times)	[92]
Bo/R8dGR	PNs	Curcumin/cisplatin	156.25 ± 14.21	DiR in the brain tumor ↑ (1.99 times)	[93]
WGA	PNs	miR132	191	DiR in the brain ↑ (1.64 times)	[94]
AAL	PNs	BACE1 siRNA/rapamycin	129.6 ± 22.6	Brain accumulation ↑ (1.4 times)	[95]
Tat	PMs	[^{14}C]-NAC	294 ± 7.2	[^{14}C]-NAC in CSF ↑ (1.4 times)	[87]
RVG29	EXO	Curcumin	194.9	Cy7 in the brain ↑ (2.23 times)	[88]
HA	PMs	siRNA	105.7	Brain accumulation ↑ (1.31 times)	[96]
Tf	PNs	Clonidine	199.5 ± 1.36	C_{max} ↑ (1.41 times)	[97]

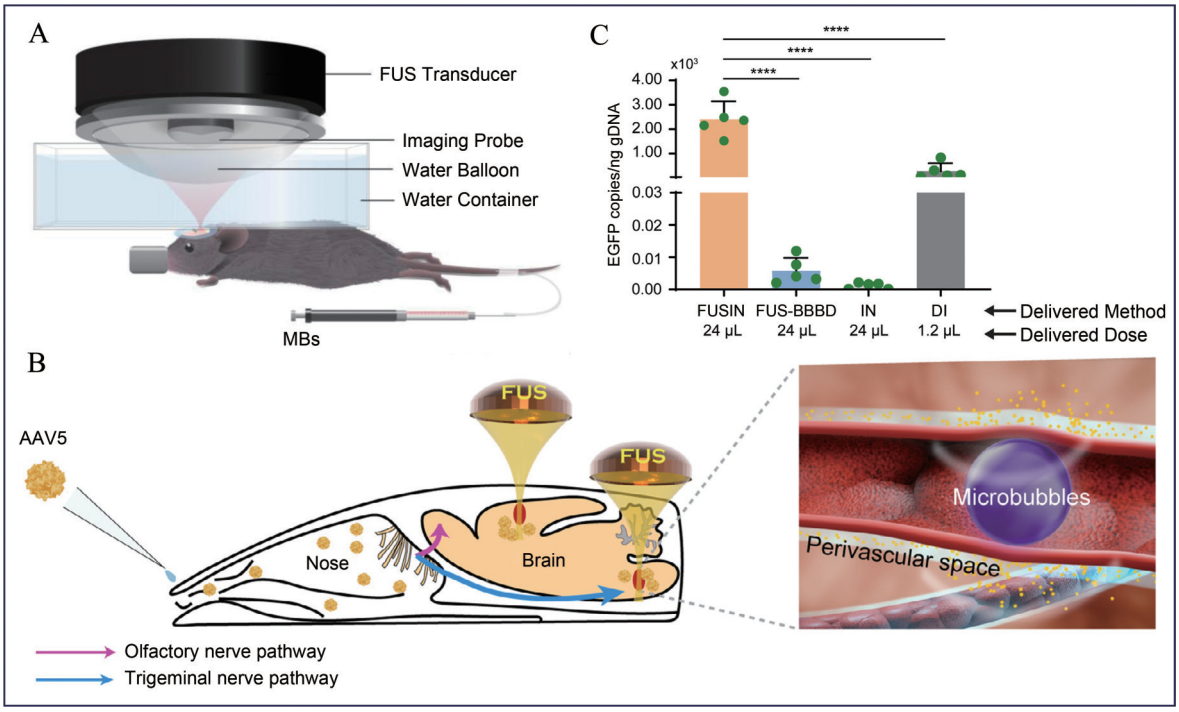

Figure 3 Schematic and classic example of FUSIN. A: Schematic of the FUS system. Adapted from Ref. 105 with permission. Copyright © 2020 Elsevier; B: Illustration of FUSIN of AAV5-hSyn-EGFP to the mouse brain; C: Comparisons of EGFP transgene concentrations (copies per ng of gDNA) in the mouse brain for all treatment groups. Adapted from Ref. 44 with permission. Copyright © 2022 Elsevier

可以轻松绕过BBB到达大脑, 让经鼻给药治疗脑部疾病成为可能。纳米制剂的优势则较好地解决了药物鼻黏膜渗透性差、黏膜纤毛清除、鼻腔保留时间短、药物生物利用度低、酶促降解等挑战, 因此受到广泛研究。因人体研究的复杂性及伦理性, 目前经鼻入脑纳米制剂主要集中在临床前研究, 多采用小鼠脑部疾病模型开展。临床前研究涉及中枢神经系统退行性疾病、脑肿瘤、脑缺血/再灌注损伤等。表3[96,107-115]总结了经典经鼻入脑纳米制剂在脑部疾病治疗中的应用研究。

4.1 阿尔茨海默病

阿尔茨海默病 (Alzheimer's disease, AD) 是常见的神经退行性疾病之一, 起源于内嗅皮层和海马体, 并逐渐扩散到大脑皮层, 导致广泛的脑萎缩, 具有认知技能下降和记忆丧失等临床特征。产生这种疾病的主要原因涉及β淀粉样蛋白斑块和Tau蛋白的积聚[116]。治疗面临的主要困境包括BBB对药物入脑的限制及药物非特异性的脑内分布使病灶部位低于治疗水平。

Huang 等[107]将间充质干细胞衍生的外泌体 (mesenchymal stem cell-derived extracellular vesicles, MSC-EVs) 掺入水凝胶 (hydrogel, GEL) 中, 制备了智能水凝胶MSC-EVs-GEL。利用EVs的膜酶促进水凝胶降解, 可以在给药部位实现持续滞留和自发的EVs释放, 延长了MSC-EVs在鼻腔的保留时间, 同时利用外泌体的表面蛋白和携带的表面活性分子结构实现了药物对病灶部位的特异性靶向。体内靶向性实验结果表明相较于游离MSC-EVs, MSC-EVs-GEL荧光信号在脑中提高了86%, 同时发现在皮质中, MSC-EVs大多与神经元共定位, 但在小胶质细胞中分布稀疏, 实现了药物在病灶部位的积聚。药效结果表明, MSC-EVs-GEL通过减轻神经损伤和促进新生神经元来逆转5×FAD AD模型小鼠的记忆丧失, 验证了其治疗阿尔茨海默病的潜力。

Liu 等[108]以黑磷 (black phosphorus, BP) 为药物载体和抗氧化剂, 并负载Tau聚集抑制剂亚甲蓝 (methylene blue, MB), 获得复合材料BP-MB, 最后将其掺入水凝胶中获得热敏水凝胶BP-MB@Gel。BP-MB@Gel鼻腔注射后, 会经历溶胶−凝胶相变并延长其在鼻腔中的停留时间, 提供高鼻黏膜保留率和可控的药物释放。体内靶向性实验证明药物主要在与AD密切相关的海马和内嗅皮质中集中, 实现了药物在病灶部位的特异性分布。药代动力学研究表明与MB组相比, BP-MB@Gel组C_{max}提高1.18倍, AUC_{0-t}提高6.47倍, BP-MB@Gel的脑靶向效率 (drug targeting efficiency, DTE) 达54.79%, 鼻−脑直接运输百分比 (nose-to-brain direct transport percentage, DTP) 达到98.55%。药效结果显示, BP-MB@Gel组显著抑制了Tau积累、恢复了线粒体功能并减轻了神经炎症, 由于

Table 3　Typical nose-to-brain nanopreparations for brain diseases therapy. DTI: Drug targeting index; DTP: Nose-to-brain direct transport percentage; DTE: Drug targeting efficiency; EE: Entrapment efficiency; DL: Drug loading; PDI: Polydispersity index

Disease	Delivery systems and characterization	Overcoming intranasal-brain delivery bottlenecks	Targeting effect	Therapeutic effect	Ref.
Alzheimer's disease	MSC-EVs-GEL Size: 120 nm Zeta: −41 mV	Increased drug retention time; reduced mucociliary clearance	DiD in the brain ↑ (1.86 times)	Enhanced the spatial learning and memory function, alleviated neuronal damage and promoted neurogenesis	[107]
	BP-MB@Gel Size: 291 nm Zeta: −26.34 mV	Increased drug retention time; reduced mucociliary clearance	DTE: 54.79% DTP: 98.55% C_{max} ↑ (1.18 times) AUC_{0-t} ↑ (6.47 times)	Protected cells from oxidative damage, ameliorated mitochondrial dysfunction, inhibited Tau accumulation and reduced neuronal apoptosis	[108]
Parkinson's disease	DA-NCPs Size: 81 ± 4.0 nm PDI: 0.124 EE (%): 69.7 ± 7.2	Reduced enzymatic degradation; improved bioavailability	DA in the brain ↑ (6 times)	Attenuated motor alterations in a 6-OHDA-induced animal model of PD	[109]
	MAG-NCs@Gel Size: 81.57 ± 1.48 nm PDI: 0.11 ± 0.02	Increased drug retention time; reduced mucociliary clearance	DTE: 809.98% DTP: 87.65% AUC_{0-t} ↑ (3.38 times) C_{max} ↑ (3.99 times)	Normalized ROS and adenosine triphosphate (ATP) in the mitochondria of dopaminergic neurons	[110]
Epilepsy	LTG-PNPs Size: 170.0 ± 2.8 nm Zeta: −16.60 ± 2.96 mV EE (%): 71.3 ± 2.0	Increased drug retention time; improved bioavailability	AUC_{0-480} ↑ (15.8 times) C_{max} ↑ (1.37 times) DTI: 984.17% DTP: 92.03%	Reduced frequency and delayed onset of epileptic seizures	[111]
	BSA-LDHs-PHT Size: 146.5 ± 3.2 nm Zeta: −16.6 ± 0.1 mV DL (%): 34.86	Improved bioavailability	Cy5.5 in the brain ↑ (2 times)	Improved the latency of seizures in the pentylenetetrazole-induced mouse models	[112]
Gliomas	HA/DP7-C/siRNA Size: 105.7 nm Zeta: −24.6 mV	Reduced enzymatic degradation; promoted mucosal penetration	Cy5 in the brain ↑ (1.31 times)	Prolonged the survival time and decreased the tumor volume	[96]
	NTMZ (NE) Size: 220−260 nm Zeta: −46.60 ± 2.79 mV	Increased drug retention time; improved bioavailability	C_{max} ↑ (2.8 times)	Promoted a reduction in vascular proliferation and lymphocytic infiltration	[113]
Cerebral ischemia/ reperfusion injury	Bo-TSA-NP Size: 160 nm Zeta: −36 mV EE (%): 70% DL (%): 3.6%	Promoted mucosal penetration	16 HBE cell uptake ↑ (1.63 times)	Improved the preventive effect on a rat model of CIRI, decreased cerebral infarction areas	[114]
Depression	BDNF-Quercetin nanogels Size: 76.34 ± 2.34 nm Zeta: −14.48 ± 0.90 mV	Increased drug retention time; reduced mucociliary clearance	C_{max} ↑ (2.33 times)	Reversed despair behavior in stress-induced mice	[115]

这些协同作用, AD小鼠模型表现出与正常小鼠相当的记忆和认知能力。

4.2　帕金森病

帕金森病 (Parkinson's disease, PD) 是仅次于阿尔茨海默病的第二大常见神经退行性疾病[117]。临床多表现为静止时震颤、运动徐缓、强直和姿势不稳定。其主要产生原因为多巴胺能黑质纹状体系统受损导致的运动活动恶化[118]。尽管有针对帕金森病的对症治疗方案, 但最终患者会因为疾病的发展而出现渐进性残疾和丧失独立性[119], 而经鼻入脑的纳米制剂为PD的治疗提供了新思路。

García-Pardo等[109]将多巴胺 (dopamine, DA) 负载于配位聚合物纳米颗粒形成稳定的胶体悬浮液 (DA nanoscale coordination polymers, DA-NCPs)。DA-NCPs的纳米结构有利于增强神经递质在细胞内的滞留。体内分布研究结果显示, DA-NCPs从右侧脑室分布到周围神经组织主要发生在前2 h内, 在右侧纹状体中观察到DA水平显著增加, 约游离药物6倍。表明药物能有效地经鼻入脑吸收, 药效研究结果表明, 在6-羟基多巴胺 (6-hydroxyDA, 6-OHDA) 诱导的PD动物模型中, DA-NCPs能有效地将DA递送到黑质纹状体通路, 显著减轻阿朴吗啡诱导的6-OHDA损伤大鼠的旋转行为。

Tan等[110]通过将厚朴酚–纳米晶体 (magnolol-

nanocrystals, MAG-NCs) 与非侵入性热敏聚合物复合并自凝胶化, 设计了温敏性水凝胶 (MAG-NCs@Gel)。实验结果表明制备的MAG-NCs@Gel在药物溶解度、鼻腔停留时间和脑靶向效率等方面明显提高, DTE高达809.98%, DTP高达87.65%, 相较于未凝胶化制剂, 脑部AUC增加约3.38倍。药效结果证明MAG-NCs@Gel能够使多巴胺能神经元线粒体中的活性氧和三磷酸腺苷正常化, 从而逆转线粒体功能障碍并改善PD小鼠的运动行为, 而不会对正常组织产生不利影响。

4.3 癫痫

癫痫是一种由大脑皮层细胞过度活动引起的神经系统疾病, 尚无有效的治疗方法, 仅可通过药物控制其发作[120]。通过常规途径 (口服、静脉内、肌肉内) 递送抗癫痫药物时常出现生物利用度低等问题, 而鼻腔给药和纳米药物的结合提供了一种绕过血脑屏障, 从而治疗癫痫发作的实用方法。

Shah等[111]通过乳化溶剂蒸发法制备了载有拉莫三嗪 (lamotrigine, LTG) 的PLGA纳米粒 (LTG-PNPs), 药物LTG可抑制钠离子通道, 从而维持神经元膜电位, 抑制兴奋性神经递质谷氨酸的释放, 有效地降低癫痫发作频率。生物分布和药代动力学研究表明, 经鼻给药后, 与对照组相比, LTG-PNPs组脑内LTG积累更多, 药物脑部AUC相较于游离LTG提高15.8倍, DTI高达984.17%, DTP高达92.03%。药效学研究则表明LTG-PNPs能显著延迟癫痫发作时间, 约是对照组3.6倍。

Zhang等[112]则通过共沉淀−水热法制备了负载苯妥英 (phenytoin, PHT) 的氢氧化物纳米粒 (phenytoin loaded layered double hydroxide nanoparticles, BSA-LDHs-PHT), 用于控制癫痫发作。体外药物释放实验表明BSA-LDHs-PHT能够快速且持续地释放药物, 这对于急性癫痫控制和慢性癫痫治疗至关重要。体内生物分布实验表明, 鼻腔给药15 min后, BSA-LDHs-Cy5.5组的荧光强度是BSA-Cy5.5组的2倍。其提高入脑效率的原理为LDH纳米粒的氢氧化物层可以保护负载药物免受酶促降解, 从而提高药物释放效率, 减少脱靶效应, 同时药物可能通过嗅觉通路的细胞外途径达到快速入脑的效果。药效结果证明给药30 min后, 小鼠模型中BSA-LDHs-PHT组癫痫发作潜伏期 (药物诱导后第一次癫痫的时间) 比游离给药组延长了近2倍。

4.4 神经胶质瘤

神经胶质瘤是颅内常见的恶性肿瘤之一, 发病率和死亡率高。起源于星形胶质细胞的胶质母细胞瘤 (glioblastoma, GBM) 是最常见的神经胶质瘤, 被世界卫生组织归类为4级肿瘤[121]。目前, GBM的最佳治疗方案包括手术、化疗和放疗。近年来, 经鼻入脑纳米制剂被认为是一种很好的神经胶质瘤治疗的非侵入性策略, 得到了广泛研究。

小干扰RNA (siRNA) 是一种潜在的基因沉默技术, 可用于治疗多种中枢神经系统疾病, 但其递送存在易被酶降解等困难。Yang等[96]利用透明质酸 (hyaluronic acid, HA) 包裹一种利于形成自组装胶束的抗菌肽 (cholesterol-modified antimicrobial peptide DP7, DP7-C), 开发了核壳结构纳米胶束HA/DP7-C递送siRNA。实验结果表明, 其具有适合鼻内给药的理化特性, 细胞摄取效率高, 细胞毒性低, 在鼻腔给药后数小时内通过三叉神经途径到达中枢神经系统。HA和CD44的相互作用增加了肿瘤部位HA/DP7-C/siRNA的积聚, 荧光强度为未修饰HA组1.31倍。此外, HA/DP7-C/siRNA可以通过沉默VEGF和LK1抑制新血管的形成或诱导肿瘤细胞凋亡, 显著减少了肿瘤体积并延长荷瘤小鼠的存活时间。

Michels等[113]成功开发了一种用于化疗药物替莫唑胺 (temozolomide, TMZ) 的新型热响应纳米乳剂 (TMZ-loaded nanoemulsion, NTMZ), 具有适合鼻腔给药的理想特性, 包括足够的TMZ浓度、合适的纳米尺寸等, 并且可以增加制剂在鼻腔区域的停留时间及延长药物释放和提高渗透。分布研究表明, 通过鼻腔给药, NTMZ在脑部的浓度较高, 是游离给药组TMZ的2.8倍, 而进入体循环的浓度则较低。药效实验证明NTMZ显著抑制了肿瘤生长。

4.5 其他

经鼻给药脑靶向纳米制剂除在上述脑部疾病临床前模型中显现出较好的治疗作用, 也在其他脑部疾病中得到广泛研究。脑缺血/再灌注损伤 (cerebral ischemia/reperfusion injury, CIRI) 发生在缺血性脑卒中患者接受快速脑血液再灌注治疗时, 这是缺血性脑卒中的标准治疗方法, 且没有其他有效的替代疗法。Wang等[114]开发了冰片修饰的丹参酮IIA纳米颗粒 (borneol modified tanshinone IIA nanoparticles, Bo-TSA-NPs), 一种新型冰片修饰的丹参酮IIA纳米粒, 比较了以不同方式修饰Bo的NPs经鼻给药后的脑靶向性能, 发现Bo化学修饰组具有更好的脑靶向效果, 能降低脑组织丙二醛含量, 提高超氧化物歧化酶活性, 减少脑梗面积, 明显改善大鼠CIRI模型的神经功能评分。抑郁症是一种威胁生命的精神疾病, 目前的药物治疗效果有限。Xu等[115]开发了负载脑源性神经营养因子的槲皮素纳米凝胶, 对慢性轻度不可预测刺激的大鼠表现出抗抑郁作用。其作用机制被证明可能与PI3K-Akt和

BDNF-TrkB信号通路的调节有关。此外, 在神经炎症、缺血性脑病等疾病治疗方面也有经鼻给药纳米制剂的相关报道[122,123]。

5　经鼻入脑纳米制剂优势与局限

5.1　绕过BBB并实现脑靶向

经鼻给药途径和其他途径相比, 具有非侵入性、给药方便、无痛和生物利用度高等优势。首先嗅觉和三叉神经通路等可让药物直接进入大脑, 绕过了BBB对药物递送入脑的阻碍, 从而提高了药物的生物利用度, 最大程度地降低外周毒性[124]。同时经鼻给药可以避免蛋白质和多肽等生物制药在胃肠道失活和肝脏快速代谢情况。在此基础上, 纳米制剂可发挥减少黏膜纤毛清除, 增强药物渗透性和生物利用度, 主动靶向大脑, 防止药物酶促降解等优势, 助力脑部疾病的治疗。随着目前纳米载体表面特定配体的修饰, 使其具有了更好的靶向效果。同时, FUS技术和外泌体的应用可以使纳米制剂达到特定的脑部区域而非全脑, 有望进一步提高脑肿瘤和各类神经退行性疾病的治疗效果。

5.2　给药量及入脑效率限制

相较于口服和静脉注射等给药方式, 经鼻入脑纳米制剂的局限之一在于其给药量受限, 过多的给药量会影响鼻腔正常功能, 这使得通过该给药途径进行脑部疾病治疗可能只能用于强效药物, 因为给药量的限制, 对于经鼻入脑纳米制剂载药量的提升显得至关重要。在给药量一定的情况下, 制剂的入脑效率则是限制其发挥药效的另一原因。同时由于快速的黏液纤毛清除机制, 缩短了药物可被吸收的时间[125]。呼吸区域具有最大的表面积并且高度血管化, 药物容易吸收到体循环, 这对入脑效率也提出了挑战[126]。目前研究较广、入脑效率较高的经鼻入脑制剂是ISG, 其能够显著延长纳米制剂在鼻腔内的保留时间[127], 同时可以联合LNP、NC等递药系统, 产生协同作用, 进一步提高入脑效率[128]。此外, 将各类纳米递药策略联合FUSIN, 也能极大提高经鼻入脑的药物含量[44,129]。因此随着纳米技术的发展, 经鼻入脑效率有望得到进一步提高。

5.3　工业化生产及临床应用困境

尽管经鼻入脑纳米制剂存在诸多优势, 在一定程度可以解决许多药物递送入脑困难的问题, 但从药物开发的角度来看, 纳米制剂较为复杂的制备流程极大增加了工业生产的难度。此外, 经鼻入脑需要将药物沉积在鼻腔黏膜区域, 以便更多的药物通过嗅觉/三叉神经等途径转运到大脑, 这使得制剂需要一个鼻腔输送装置来实现有效的药物递送, 为探索新型鼻–脑递送装置, 以高效地将潜在药物输送到大脑, 需要进行更多的尝试。同时现阶段所报道的研究应用工作多为临床前研究, 虽然常用的啮齿类动物模型和人类鼻腔结构具有广泛的相似性, 但在嗅上皮比例方面存在显著差异[130], 所以将动物模型研究成果转化到临床亦是一个巨大的挑战, 需要准确的临床转化模式与方法。并且经鼻入脑纳米制剂的综合质量评价体系也尚未建立, 因此从实验室研究到临床应用还有大量工作需要完成。

6　小结与展望

随着纳米技术的蓬勃发展, 越来越多的经鼻入脑纳米制剂因其独特优势被用于脑部疾病治疗研究。本综述系统总结了经鼻入脑纳米制剂的递送通路及转运机制, 提高经鼻入脑递送效率的方法, 各类纳米递药策略及其在相关疾病模型中的应用, 并探讨了目前研究与应用的困境。虽然经鼻入脑纳米递药策略取得了阶段性成就, 但也仍然存在一些问题, 如快速的黏液纤毛清除机制导致入脑效率不高; 缺乏经鼻入脑纳米制剂的综合质量评价体系; 制剂鼻腔给药的安全性评价方式不明确; 对特定脑区及特定致病细胞的精准靶向研究较少。此外, 经鼻入脑纳米制剂的经济效益也值得关注。解决以上问题有望突破该类制剂的临床转化及应用瓶颈。因此未来亟需建立经鼻入脑纳米制剂的综合质量评价体系和系统的安全性评价方式, 进一步研究递送效果优异、靶向性精准的新型纳米递药策略, 如基于LNP的ISG和外泌体等, 及增强入脑效率的新方式, 如FUSIN等, 同时应该强调多学科交叉融合, 探索经鼻入脑纳米递药策略发展的新方向。随着经鼻入脑纳米制剂研究的深入, 该领域有望得到进一步发展, 并逐步由相关药物制剂研究走向临床转化。

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