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超声靶向微泡破坏技术：神经退行性疾病治疗的新手段*

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摘要 神经退行性疾病（neurodegenerative diseases，NDs）是一组以神经元结构和功能进行性丧失为特征的疾病，主要表现为认知功能下降、运动能力丧失及精神行为异常等症状，包括阿尔茨海默病（Alzheimer's disease，AD）、帕金森病（Parkinson's disease，PD）和肌萎缩侧索硬化症（amyotrophic lateral sclerosis，ALS）等。随着全球人口增长和老龄化趋势的加剧，NDs的发病率持续上升，目前尚无根治方法。血脑屏障（blood-brain barrier，BBB）在保护中枢神经系统稳定性、阻止血液中有害物质进入脑组织的同时，也限制了药物向脑实质的递送，为神经退行性疾病的治疗带来了巨大挑战。超声微泡靶向破坏（ultrasound-targeted microbubbles destruction，UTMD）技术是近年来在医学领域迅速发展的新兴技术，将聚焦超声（focused ultrasound，FUS）与微泡（microbubbles，MB）造影剂相结合，瞬时且可逆地打开BBB从而增加药物透过浓度，具有高效性、安全性和靶向性等特点，在NDs诊断和治疗领域具有巨大的开发潜力。本文介绍微泡的基本特征及超声微泡开放BBB的可能机制，并对UTMD技术在NDs治疗中的研究进展进行综述，旨在为神经退行性疾病治疗新策略和药物的研发提供理论依据和研究方向。

关键词 神经退行性疾病，超声微泡靶向破坏技术，血脑屏障，药物递送，治疗
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神经退行性疾病（neurodegenerative diseases，NDs）是一组以神经元的结构和功能进行性丧失为特征的疾病，主要表现为认知功能下降、运动能力丧失及精神行为异常等症状，包括阿尔茨海默病（Alzheimer's disease，AD）、帕金森病（Parkinson's disease，PD）和肌萎缩侧索硬化症（amyotrophic lateral sclerosis，ALS）等[1-2]。世界卫生组织（World Health Organization，WHO）2023年的统计数据显示，全球NDs患者总数已超过5 500万，预计2030年将增至7 800万，2050年可能达1.5亿[3]。然而，由于血脑屏障（blood-brain barrier，BBB）限制药物递送、疾病早期诊断困难以及神经元损伤不可逆等因素，目前NDs尚无治愈手段[4-5]。因此，开发有效的NDs治疗方法是当前老龄化社会面临的一项重大公共卫生挑战。

超声靶向微泡破坏（ultrasound-targeted microbubbles destruction，UTMD）技术是近年来材料科学与生物工程交叉融合的新兴技术，结合了微泡载体和超声波的物理特性，可瞬时且可逆打开BBB从而增加药物透过浓度，具有靶向性强、安全性高、非侵入性以及载药性能高等优势。近年来，UTMD在肿瘤、肝脏疾病及心血管疾病的诊断和治疗方面的研究已成为热点[6-8]。本文主要介绍超声微泡的基本特征、UTMD技术开放BBB的可能机制以及不同超声参数对BBB的影响，重点综述UTMD技术治疗不同神经退行性疾病在基础及临床转化方面的研究进展，以期为NDs的治疗提供新的策略。

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1　超声微泡概述

超声微泡（ultrasound microbubble）由气体核心及生物相容性外壳两个关键部分组成（图1）。气体核心主要为全氟化碳或六氟化硫，空气和氮气等次之，外壳则由脂质、蛋白质、高分子聚合物等材料构成[9]。根据直径大小，超声微泡可分为微米微泡和纳米微泡。其中，直径为1~10 μm的微泡造影剂广泛应用于临床超声检查[10]。Sono Vue®、Definity®（全氟类气体为核心，磷脂为外壳）和Optison®（全氟类气体为核心，蛋白质为外壳）是目前已被美国食品药品监督管理局（Food and Drug Administration，FDA）批准可用于临床诊疗的微泡造影剂[11]（表1）。

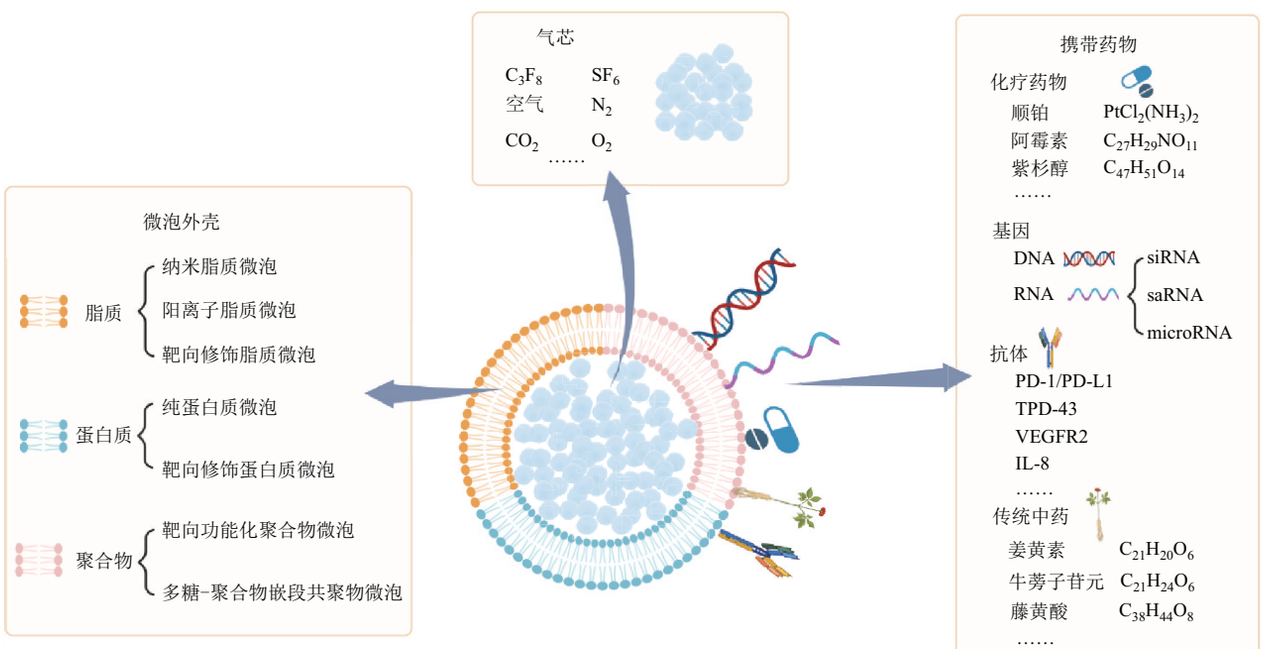

Fig. 1　Microbubble structure diagram

图1　微泡结构示意图

PD-1/PD-L1：程序性细胞死亡蛋白1/程序性细胞死亡蛋白配体1（programmed cell death protein 1/programmed cell death-ligand 1）；TDP-43：TAR DNA结合蛋白43（TAR DNA-binding protein 43）；VEGFR2：血管内皮生长因子受体2（vascular endothelial growth factor receptor 2）；IL-8：白介素-8（interleukin-8）。

1968年，Gramiak和Shah[12]将微泡应用于人体心脏超声检查，他们观察到微泡注射后主动脉根部的超声信号显著增强，为微泡造影剂与超声波的联合应用奠定了基础。1996年，Mahabadi研究团队[13]首次证实，脂质微泡可有效负载紫杉醇等疏水性化疗药物，经过超声作用实现药物的可控释放，使靶区药物浓度较常规给药提升4~7倍，从此开创了超声微泡的诊疗一体化应用。随着研究的不断深入，超声微泡的载药种类从传统的化疗药物扩展到核酸药物、抗体药物和中药单体化合物[14]。同时，其载药策略从最初的被动物理吸附优化为更加稳定的化学修饰，递送方式也从被动扩散演进为主动靶向递送[15-16]。

Table 1　Types and properties of microbubbles

表1　微泡类型及特性

微泡类型	外壳成分	特点	实验阶段微泡	商品化微泡
脂质微泡	纳米脂质微泡、阳离子脂质微泡、靶向修饰脂质微泡	稳定性更优、免疫原性低[17]，构成脂质体的磷脂膜可生物降解，对人体无害，但生物活性修饰灵活性较低[18]	Esc微泡[19]、RC5k微泡[20]、Ab-MMB1532[21]	Definity®、Sono Vue®、Sonazoid®[22]
蛋白质微泡	纯蛋白质微泡、靶向修饰蛋白质微泡	弹性和黏度更高，瞬态空化阈值较大，需更高声能触发[23]	SDF-1α微泡、GPVI-Fc微泡、Optison™、Albunex®[24] Aβ1-42微泡[14]	

续表1

微泡类型	外壳成分	特点	实验阶段微泡	商品化微泡
聚合物微泡	靶向功能化聚合物微泡、多糖-聚合物嵌段共聚物微泡	粒径分布集中、体内稳定性好、共振频率较高，在较高的发射频率时可获得理想的散射强度[25]	CM-Dextran微泡、Dextran微泡、Fucoidan微泡[26]	无
其他	脂质-蛋白质复合微泡、蛋白质-聚合物混合微泡、脂质-聚合物混合微泡	稳定性高、靶向性高，体内循环时间长[27]，载药量显著提高，可控释药能力强[14]	PBCA微泡[28]、PLGA+DSPE-PEG脂质微泡、PCL+DSPE脂质微泡[29]	无

2　超声靶向微泡破坏技术

1998年，Price等[30]首次提出了UTMD技术的概念。他们利用超声诱导的微泡空化效应在血管内皮上形成可逆性裂隙，成功实现了胶体颗粒和红细胞的跨血管递送，为后续UTMD的广泛应用奠定了理论基础。相较于其他递送方法，UTMD具有多方面的优势，主要体现在以下几方面。a. UTMD可短暂可逆地增强细胞膜通透性，研究表明[31]，超声作用后细胞膜的通透性可在1~3 h恢复正常，BBB的通透性在6~24 h内可恢复正常[32]。此外，微泡常用的生物相容性外壳可被机体代谢，无长期蓄积的风险[33]。b. UTMD不仅能显著提高药物递送效率[34]，微泡还可同时作为超声造影剂和治疗载体，实现诊疗一体化[35]。c. UTMD技术具有空间靶向性和分子靶向性双重优势，可以实现药物的精准递送[36]。一方面，通过特定区域超声场的作用，微泡选择性地在靶区破裂并释放药物（空间靶向性）。另一方面，微泡可借助表面偶联抗体、配体或多肽等修饰技术实现主动靶向递药（分子靶向性）。d. UTMD只需常规超声设备，微泡制备的原料易得且合成工艺简单，无论是应用于检查还是治疗，成本都相对较低[37]。综上所述，UTMD技术因其安全性、高效性、靶向性和低成本等优势，在心血管疾病、神经系统疾病及恶性肿瘤等重大疾病的诊断与治疗中展现出广阔的应用前景。

3　UTMD开放BBB

3.1　BBB

BBB是中枢神经系统与血液循环系统之间的重要屏障，主要由毛细血管内皮细胞、基底膜和星形胶质细胞组成[38]。1959年，Davson和Spaziani等[39]发现脑毛细血管能够阻止碘化物、p-氨基马尿酸盐和蔗糖等物质扩散到大脑，而氧气、二氧化碳和水则可以跨越BBB，首次证实了BBB的选择性透过机制。毛细血管内皮细胞的紧密连接和黏附连接共同维持BBB结构的完整性，选择性地滤过进入大脑实质的物质[40]。跨膜蛋白Claudins、Occludin和细胞骨架相关蛋白ZO-1协同作用，形成高度复杂的物理屏障，实现BBB的电荷选择性限制，E-cadherin则实现BBB的大小选择性限制[32]。BBB是维持中枢神经系统稳态的关键结构基础，使大脑实质免受病原体、毒素、炎症因子等有害物质的损伤[41]。然而，BBB的生理屏障特性为中枢神经系统药物递送带来显著挑战。研究表明，超过98%的小分子药物和几乎100%的大分子药物无法通过BBB到达大脑实质[42]，为药物治疗中枢神经系统疾病带来了巨大挑战。

3.2　UTMD开放BBB的作用机制

2001年，Hynynen等[43]将微泡造影剂经兔子耳静脉注入体内，在其大脑部位超声处理5 min后，通过磁共振成像（magnetic resonance imaging，MRI）进行48 h实时监测和定位，首次证明了超声联合微泡技术可在不损害周围神经元的情况下安全、可逆地打开兔子的BBB，此技术为中枢神经系统疾病靶向药物的递送提供了重要的研究基础。UTMD开放BBB的作用机制主要与空化效应和声孔效应有关。空化效应分为稳定空化和惯性空化，低强度超声（0.3~3 W/cm²）作用微泡后产生稳定空化效应，微泡周围介质出现声学微流，对附近的细胞或血管壁施加剪切应力从而拉伸细胞膜和毛细血管壁[44]，短暂地破坏紧密连接蛋白[45]，增加BBB的通透性；高强度超声（大于3 W/cm²）作用微泡后产生惯性空化效应，产生高强度冲击波和高速液体射流[34]，同时在局部形成热力学环境，诱导声化学反应生成自由基，从而为大分子药物提供短暂且可逆的通道[46]。声孔效应则会导致血流中的微泡破裂，在周围血管壁或细胞表面造成可逆或不可逆的穿孔[47]，增强药物的被动扩散及主动转运，最终提高目标区域的药物浓度[48]，增强药物递送浓度及治疗效果（图2）。

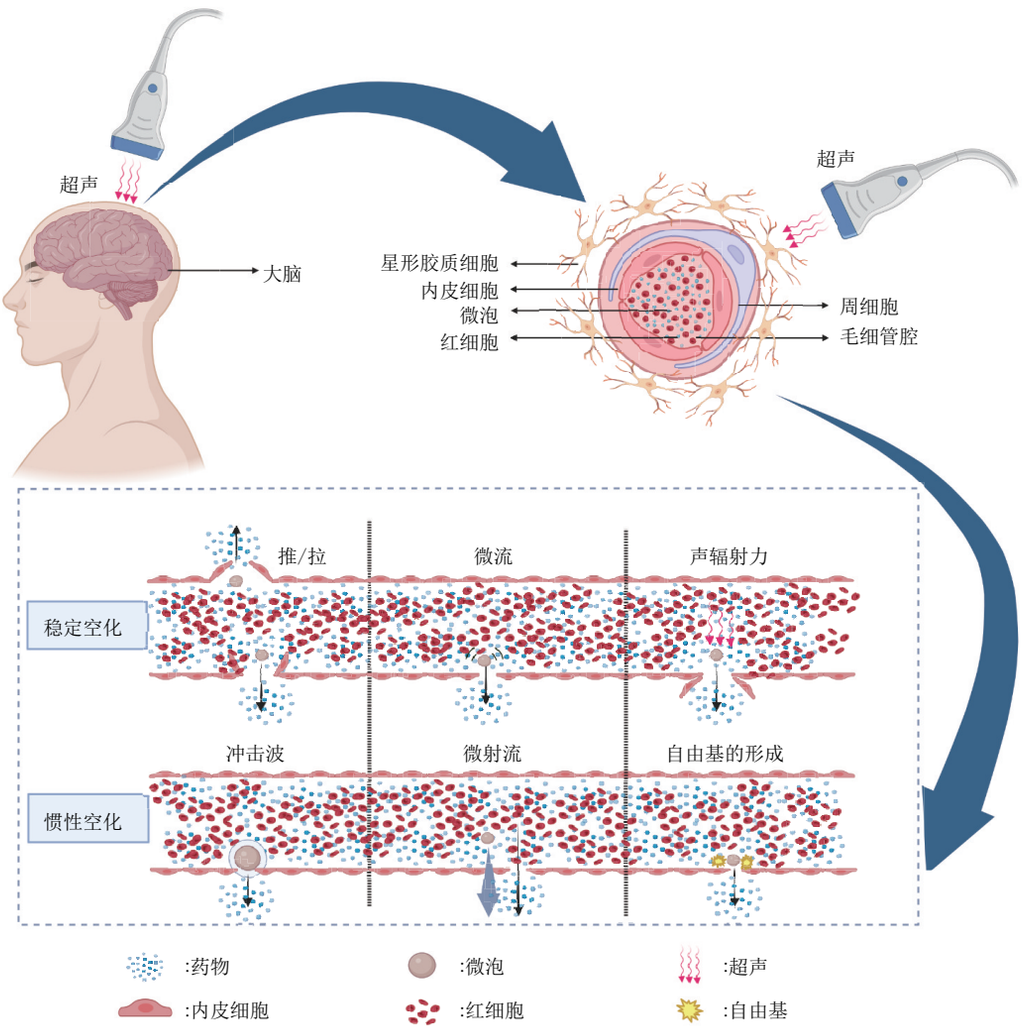

Fig. 2　Diagram of UTMD opening the BBB mechanism

图2　UTMD开放BBB机制图

3.3　超声微泡特性与超声参数对BBB的影响

超声微泡的特性及超声参数是影响BBB通透性的重要因素[49]。2024年，Guo等[50]比较了外壳较硬的蛋白质微泡Optison®和外壳更具弹性的脂质微泡Definity®对BBB的影响，研究发现，脂质外壳的微泡更易打开BBB。微泡的粒径决定了循环半衰期、跨血管分布能力以及诱发超声空化的阈值和强度。研究发现，4~5 μm微泡在0.30 MPa时，BBB渗透率指标可达0.15 min^{-1}，而1~2 μm微泡在相同压力下几乎无响应，需0.45 MPa以上才能达到类似效果[51]。微泡的表面电荷会影响其与血管内皮细胞的相互作用，其中带正电荷的微泡可通过静电作用增强与内皮细胞的黏附能力[52]，从而更有效地在靶部位积聚，并促进BBB的开放。微泡表面还可修饰特异性配体后，可通过主动识别并结合脑血管内皮细胞上的特定受体[53]，显著提升BBB开放的空间靶向性与递送效率，同时降低对非靶组织的损伤。此外，超声处理时间、超声频率、脉冲重复频率（pulse repetition frequency，PRF）、声强等超声参数也会影响BBB的开放程度[54]：当超声暴露时间从30 s增加到300 s时，BBB的破坏程度显著增加[55]。Shumer-Elbaz等[56]发现，相比传统高频超声，850 kHz在125~500 kPa范围内低频超声可增强颅骨穿透性，减少组织衰减，同时优化微泡振动响应，实现安全BBB开放。当PRF从1 Hz增加到5 Hz时，MB的谐波发射增强，BBB开放程度增加，且组织损伤减少[57]。因此，调整微泡组成并优化超声参数，可最大限度地避免组织损伤的同时确保BBB的有效开放，调节输送到脑实质的药物剂量。

4　UTMD在神经退行性疾病中的应用

UTMD技术作为近年来一种新兴的非侵入性治疗策略，在神经退行性疾病领域展现出显著的应用潜力。该技术通过联合聚焦超声（focused ultrasound，FUS）和微泡造影剂，实现BBB的可逆性开放和靶向药物递送，为AD、PD和ALS等疾病的治疗提供新的解决方案（表2）。

Table 2　The application of ultrasound-targeted microbubbles in various neurodegenerative diseases

表2　超声靶向微泡在不同神经退行性疾病中的应用

疾病类型	实验对象	递送物质	超声参数	主要结果	参考文献
阿尔茨海默病	TgCRND8小鼠	空微泡	*FF*=1.68 MHz，*PRF*=1 Hz，*PD*=10 ms，*SD*=120 s	改善Tg小鼠的空间记忆能力，减少脑内Aβ斑块数量和大小，促进小鼠海马体中新生神经元的生长	［58］
	TgCRND8小鼠	空微泡	*FF*=1.1 MHz，*PRF*=1 Hz，*PD*=10 ms，*SD*=120 s，*ISP*=0.4~0.8 MPa	超声处理后2 d显著降低小鼠海马体中的Aβ斑块体积，每两周3~5次FUS治疗后，海马体中的斑块数量和表面积显著减少	［59］
	TgCRND8小鼠	IVIg	*FF*=1.68 MHz，*PRF*=1 Hz，*PD*=10 ms，*SD*=120 s	减少小鼠脑内Aβ斑块的数量，增加海马体细胞的数量，降低海马体内TNF-α水平	［60］
	5×FAD小鼠	空微泡	*FF*=715 kHz，*PRF*=1 Hz，*PD*=20 ms，*SD*=60 s，*DC*=2%	小鼠脑内Aβ和tau蛋白的沉积显著减少，改善小鼠的认知障碍	［61］
	5×FAD小鼠	ADU	*FF*=0.5 MHz，*PRF*=1 Hz，*PD*=10 ms，*SD*=120 s，*PPA*=0.25 MPa	减少脑内Aβ斑块的沉积，改善小鼠的认知功能障碍	［62］
	5×FAD小鼠	抗Aβ抗体	*FF*=1 MHz，*PD*=10 ms，*SD*=100 s，*DC*=1%，*AP*=6.5~22.8 W，*ISP*=0.3~0.6 MPa	FUS单次处理后，瞬时破坏BBB，特异性抗Aβ抗体被递送至小鼠脑内	［63］
	rTg4510小鼠	空微泡	*FF*=1.5 MHz，*PRF*=10 Hz，*PD*=6.7 ms，*PNP*=0.45 MPa，*SD*=60 s	FUS处理的脑区内，p-tau水平显著降低，未接受超声照射的对侧脑区，p-tau水平也出现了一定程度减少	［64］
	3×Tg-AD小鼠	空微泡	*FF*=0.996 MHz，*PRF*=1 Hz，*PD*=10 ms，*PRPA*=0.64 MPa	改善小鼠的记忆力和学习能力，降低小鼠海马体中Aβ和磷酸化tau蛋白，促进小鼠小胶质细胞对Aβ的吞噬	［65］
	APP/PS1小鼠	Qc@SNPs	*PNP*=1 000 kPa，*SD*=600 s	减少神经元凋亡、炎症反应、钙稳态失衡和氧化应激，显著改善AD小鼠的学习能力和记忆能力	［66］
	P301S小鼠	07/2A mAb	*PRF*=2 Hz，*PD*=10 ms，*SD*=100 s	增加小胶质细胞的免疫活性及中性粒细胞/单核细胞的浸润	［67］
	AD患者	空微泡	*FF*=220 kHz，*PD*=2 ms，*SD*=50 s，*PNP*=0.3~0.6 MPa，*DC*=0.74%	可实现局部BBB的重复开放，术后3个月患者淀粉样蛋白负荷未出现统计学差异，患者认知评分未出现临床显著恶化或改善	［68］
	AD患者	空微泡	*FF*=220 kHz	FUS作用后靶区BBB在24 h内完全闭合，与未治疗脑区相比，靶区Aβ负荷变化差异不显著	［69］
	AD患者	空微泡	*FF*=220 kHz，*SD*=60 s	AD患者额叶区域Aβ沉积减少，临床症状和神经心理学测试分数的短暂改善	［70］
帕金森病	SD大鼠（颅内注射6-OHDA诱导为PD模型大鼠）	Nrf2	*FF*=0.5 MHz，*SD*=30 s	抑制ROS的产生，保护PD大鼠的神经元	［71］
	C57小鼠（腹腔注射MTPT诱导为PD模型小鼠）	CPC/PS 80 NPs	*FF*=1.281 9 MHz，*SD*=60 s	改善PD小鼠的运动障碍，恢复小鼠多巴胺能神经元功能	［72］
	BALB/c小鼠（腹腔注射MTPT诱导为PD模型小鼠）	BDNF或GDNF	*FF*=1.0 MHz，*PRF*=10 Hz，*PD*=10 ms，*SD*=180 s	促进GDNF或BDNF表达，保护纹状体神经元	［73］

续表2

疾病类型	实验对象	递送物质	超声参数	主要结果	参考文献
	C57小鼠（腹腔注射MTPT诱导为PD模型小鼠）	Q@CE-BG	*FF*=1.0 MHz，*SD*=120 s，*DC*=20%，*I*=1.5 W/cm^2	改善PD小鼠的运动功能障碍和空间记忆障碍，神经元丢失减少，TGF-β1表达上调，改善大脑微环境	[74]
	PD患者	空微泡	*FF*=220 kHz	第二次FUS治疗后的3~4周，MoCA测试、视觉记忆以及执行和视觉空间功能都有所改善	[75]
肌萎缩侧索硬化症	G93A-SOD1小鼠	依达拉奉	*FF*=1.1 MHz，*PRF*=1 Hz，*PD*=9.09 ms，*SD*=60 s，*PRPA*=0.52 MPa	改善小鼠的神经肌肉功能，减轻神经炎症并减少错误折叠的SOD1蛋白	[76]
	G93A-SOD1小鼠	Arc	*FF*=1.1 MHz，*PRF*=1 Hz，*PD*=10 ms，*SD*=60 s，*PRPA*=0.6 MPa，*ISP*=0.49 MPa	改善小鼠运动功能障碍，减轻腓肠肌的萎缩程度，减少神经元萎缩	[77]
	G93A-SOD1小鼠	SOD1 ASOs	*FF*=250 kHz，*PRF*=1 Hz，*PD*=10 ms，*SD*=30 s	降低小鼠大脑中SOD1的蛋白质表达，增加运动神经元的数量，减少运动神经元的变性	[78]
	ALS iBEC	抗TDP-43	*FF*=286 kHz，*PD*=20 ms，*SD*=120 s，*PRPA*=0.3 MPa	促进抗TDP-43抗体跨越BBB，降低IL6和TNF-α的表达	[79]
	ALS患者	空微泡	*FF*=220 kHz，*PRF*=300 ms，*DC*=0.88%	FUS可介导BBB的可逆性开放，患者认知或痉挛状态没有显著改变	[80]

TgCRND8小鼠：广泛用于阿尔茨海默病研究的转基因动物模型，可快速、大量地形成Aβ斑块，模拟人类AD的核心病理小鼠；5×FAD小鼠：早期痴呆模型小鼠；rTg4510小鼠：广泛使用的tau蛋白病变转基因小鼠模型；3×Tg-AD小鼠：同时携带APP、PS1和tau突变的三重转基因小鼠；APP/PS1小鼠：携带APP、PS1突变的转基因小鼠；P301S小鼠：表达人类突变tau蛋白的转基因阿尔茨海默病模型小鼠；C57小鼠：常用的近交系实验小鼠；BALB/c小鼠：广泛使用的近交系实验小鼠；SD大鼠：研究中常用的远交系实验大鼠；G93A-SOD1小鼠：表达SOD1的G93A突变体，模拟ALS的神经退行性病理模型小鼠；iBEC：多能干细胞来源的脑微血管内皮细胞（induced pluripotent stem cell-derived brain endothelial cells）。FUS：聚焦超声（focused ultrasound）；IVIg：静脉注射免疫球蛋白；TNF-α：肿瘤坏死因子-α（tumor necrosis factor-α）；ADU：人类免疫球蛋白γ1单克隆抗体（aducanumab）；p-tau：磷酸化Tau蛋白（phosphorylated tau protein）；Qc@SNPs：槲皮素修饰的硫纳米颗粒（quercetin modified sulfur nanoparticles）；07/2A mAb：抗-硫代谷氨酸3Aβ抗体；6-OHDA：6-羟基多巴胺，研究帕金森病和单侧运动障碍的经典模型工具；Nrf2：核因子相关因子2（nuclear factor erythroid 2-related factor 2）；MTPT：1-甲基-4-苯基-1,2,3,6-四氢吡啶，一种神经毒素，研究帕金森病的经典化学诱导模型工具；CPC/PS 80 NPs：载姜黄素聚山梨醇酯80修饰角质体纳米颗粒（curcumin-loaded polysorbate 80-modified cerasome nanoparticles）；BDNF：脑源性神经营养因子（brain-derived neurotrophic factor）；GDNF：神经胶质细胞系衍生的神经营养因子（glia cell line-derived neurotrophic factor）；Q@CEBG：封装CeO2纳米酶与槲皮素的谷胱甘肽修饰牛血清白蛋白纳米反应器；TGF-β1：转化生长因子β1（transforming growth factor-beta 1）；MoCA：蒙特利尔认知评估（Montreal Cognitive Assessment）；Arc：牛蒡子苷（arctigenin）；SOD1：超氧化物歧化酶1（superoxide dismutase 1）；ASOs：反义寡核苷酸（antisense oligonucleotides）；TDP-43：TAR DNA结合蛋白43（TAR DNA-binding protein 43）；IL-6：白介素-6（interleukin-6）；FF：基频（fundamental frequency）；I：强度（intensity）；PRF：脉冲重复频率（pulse repetition frequency）；PD：脉冲持续时间（pulse duration）；SD：声脉冲群持续时间（sonication duration）；DC：占空比（duty cycle）；ISP：峰值稀疏声压（incident sparse pressure）；PRPA：峰值稀疏压振幅（peak pare factional pressure amplitude）；PNP：峰值负压振幅（peak negative pressure）。

4.1　UTMD与AD

AD是最常见的神经退行性疾病，其病理学特征包括β淀粉样蛋白（amyloid β-protein，Aβ）沉积、tau蛋白过度磷酸化与神经原纤维缠结、突触与神经元丢失等，临床表现为进行性遗忘和认知障碍[81-82]。据统计，全球每年患AD的人数超过5 000万，其患病率随年龄增长显著上升[83]。目前，AD尚无根治方法，治疗失败的一个重要原因是常规途径给药难以穿过BBB，导致药物在脑组织内的生物利用率极低[84]。

研究表明，即使不装载治疗药物，单独使用FUS也能有效缓解AD动物模型的症状[58]。Poon等[59]进行了单次FUS治疗的长期效果评估和多次FUS治疗的累积效果评估。发现单次FUS治疗后，Aβ斑块体积在超声后两天内显著减少至原始体积的62%±16%（P≤0.001），并且这种减少可持续两周。经过3~5次FUS治疗的小鼠Aβ斑块数量减少27%±7%（P≤0.01），斑块表面积减少40%±10%（P≤0.01），表明多次FUS治疗能有效减少中度至晚期AD小鼠模型中Aβ的沉积。Lee等[61]将FUS作用于早期痴呆模型小鼠后发现，小鼠脑内可溶性Aβ的含量显著减少。此外，FUS/MB促进了Aβ从

脑实质向脑脊液（cerebrospinal fluid，CSF）的转移，小鼠的认知障碍得到明显改善。Shen等[65]则发现，UTMD处理后小鼠脑内小胶质细胞分支减少、体积增大，并直接吞噬Aβ沉积。同时，tau蛋白在Ser235/Thr231和Ser202/Thr205位点的磷酸化水平降低，显著改善了小鼠的记忆力和学习能力。

此外，Liu等[66]成功制备了槲皮素修饰的硫纳米微泡（quercetin modified sulfur nanoparticles-microbubble，Qc@SNPs-MB）。结果显示，Qc@SNPs-MB结合超声能有效打开BBB，提高药物在脑组织中的生物利用度，减少内质网应激，维持细胞内钙离子平衡，并清除活性氧类（reactive oxygen species，ROS），显著改善小鼠的学习能力和记忆能力。以上研究为UTMD技术的临床应用提供了重要依据。

2018年，Lipsman团队[68]首次开展了Definity®微泡联合聚焦超声治疗AD可行性和安全性的临床研究，研究对象为5名年龄在50~85岁之间的轻度至中度AD患者，他们使用220 kHz的聚焦超声对患者进行非侵入性治疗，试验发现5名患者均成功实现了BBB暂时、可逆性开放，24 h后发现BBB完全闭合且无不良事件发生。Meng等[69]开展了一项对9名AD患者进行磁共振引导聚焦超声（magnetic resonance-guided focused ultrasound，MRgFUS）介导BBB开放的单臂临床试验，患者接受隔周1次，共3次干预，并于6个月后随访。研究发现，此技术实现了患者双侧海马体、前扣带回及楔前叶等多个脑区的暂时性BBB开放，且未报告治疗相关不良事件。此外，Chang等[70]使用MRgFUS进行胶质母细胞瘤和AD的BBB开放的临床研究，其中5例AD患者接受了两个周期的超声治疗，间隔3个月，结果表明，AD患者额叶区域Aβ沉积减少，临床症状和神经心理学测试分数短暂改善。以上研究均表明，UTMD技术有望成为治疗AD的新策略，但超声参数与微泡特性仍是UTMD技术临床转换的重难点。因此，亟须开展严格的I/II期临床试验以评估其在AD不同阶段的安全性和初步疗效。

4.2　UTMD与PD

PD是第二大常见的神经退行性疾病，其核心病理特征为黑质多巴胺能神经元的进行性丢失[85-86]，导致运动功能障碍及其他症状，影响着全球数百万人的健康。预计到2050年，全球PD患者将达2 522.4万，较2021年增长112%[87-88]。

UTMD能有效递送基因透过BBB发挥治疗作用。核因子E2相关因子2（nuclear factor-E2-related factor 2，Nrf2）是调控细胞氧化还原平衡的核心转录因子，在PD的发生发展过程中发挥了重要作用[89]。Long等[71]制备了负载Nrf2质粒的MB，在MRgFUS引导下靶向递送Nrf2至PD模型小鼠的黑质区，结果发现，该方法可显著提升Nrf2的表达并抑制ROS产生，减少PD模型小鼠神经元的损伤。姜黄素能通过清除α突触核蛋白发挥PD治疗作用，但其生物利用度低且BBB穿透能力差，限制了临床应用[90]。Zhang等[72]开发了负载姜黄素的聚山梨酯80修饰的陶瓷体（curcumin-loaded PS 80-modified cerasome，CPC/PS 80）纳米微泡，利用UTMD技术将CPC/PS 80纳米颗粒递送到纹状体，增加了药物的递送效率，改善了PD小鼠的运动功能障碍。

神经营养因子（neurotrophic factors，NF）在减少神经元进行性变性和维持大脑发育中发挥重要作用[91]。Lin等[73]利用UTMD技术将胶质细胞源性神经营养因子（glia cell line-derived neurotrophic factors，*GDNF*）和脑源性神经营养因子（brain-derived neurotrophic factors，*BDNF*）基因递送至PD模型小鼠的脑组织，治疗后的小鼠脑内钙沉积减少，caspase-3表达下调，细胞凋亡减少。此外，神经炎症反应减轻，神经元特异性β-微管蛋白表达增加，保护小鼠多巴胺能神经元免受损失。Gao等[74]制备了封装CeO_2纳米酶与槲皮素的谷胱甘肽修饰牛血清白蛋白纳米反应器（Q@CeBG），并利用UTMD技术暂时开放BBB，显著提升了Q@CeBG在小鼠脑组织的靶向富集水平，多靶点清除ROS，缓解氧化应激，调节小胶质细胞极化，改善炎症微环境，保护PD模型小鼠多巴胺能神经元，逆转病理损伤。

2021年，Obeso及其团队[75]招募了5名平均病程为7.6年的男性PD患者进行I期临床试验。结果显示，UTMD技术成功实现了4例患者BBB的可逆性开放，受试者认知功能得到改善，且未观察到脑水肿或出血等严重不良事件。

综上所述，UTMD技术有望成为PD的精准治疗的新途径。然而，PD不同阶段对BBB开放程度和药物递送需求各异，需重点开发靶向PD相关分子的配体修饰微泡以提高特异性，并探索适用于不同治疗目标的最佳UTMD参数组合。

4.3 UTMD与ALS

ALS是一种致命的神经退行性疾病，主要累及大脑皮层、脑干和脊髓的上、下运动神经元[92]，发病率约为2.16/10万人年，患者的中位生存期仅为3~5年[93]，其病因尚未完全阐明，缺乏有效治疗手段。

研究发现，超氧化物歧化酶1（superoxide dismutase 1，*SOD1*）基因突变是ALS的重要致病因素[94-95]。Shen等[76]将自由基清除剂依达拉奉注入小鼠体内，随后靶向超声ALS模型小鼠的脑部，有效提升了依达拉奉在小鼠脑组织中的蓄积浓度，高效清除错误折叠SOD1，治疗组小鼠运动神经元存活率提高42%，并显著改善小鼠的神经肌肉功能。Zhang等[77]则利用UTMD技术将牛蒡子苷（arctigenin，Arc）递送至ALS模型小鼠的运动皮层，抑制了神经炎症反应，明显减轻了小鼠运动神经元和腓肠肌的萎缩，改善小鼠运动功能。此外，Ediriweera等[78]利用UTMD技术将负载SOD1反义寡核苷酸（antisense oligonucleotides，ASO）的纳米微泡递送至ASL模型小鼠的脑组织，ASO在靶区域高效沉默SOD1，减少错误折叠蛋白积累，治疗组小鼠脑组织中SOD1蛋白表达较对照组降低至原来的1/3以下，而脊髓运动神经元数量明显增加。TAR DNA结合蛋白43（TAR DNA-binding protein 43，TDP-43）被认为是与运动神经元变性密切相关的关键蛋白[96]。基于这一发现，Wasielewska等[79]建立了基于诱导脑内皮样细胞（induced brain endothelial-like cells，iBECs）的全人源ALS患者细胞BBB模型，发现健康对照和FUS/MB处理组的iBECs中TNF、IL-6、CCL2等促炎因子表达下调，抗TDP-43抗体递送效率提升，其中处理组的iBECs中增加2.7倍，散发性ALS的iBECs中增加1.9倍，均高于健康对照，同时处理后1 h健康对照和FUS/MB处理组的iBECs的跨内皮电阻（trans-endothelial electrical resistance，TEER）显著降低，24 h后TEER恢复甚至升高，表明UTMD技术能增加BBB的通透性并提升抗TDP-43抗体递送效率，这些临床前研究为UTMD技术用于ALS治疗提供了实验支持。

2019年，Abrahao团队[80]针对4名ALS患者开展了临床试验，研究发现所有受试者超声辐照后BBB成功开放并在24 h后恢复正常，未出现严重的临床、影像学或脑电图不良反应。

综上所述，UTMD技术可非侵入性地开放ALS患者的BBB，未来可与潜力治疗药物联用，为ALS治疗提供靶向递送平台。然而，UTMD技术在ALS中的研究尚处早期阶段且病情进展十分迅猛。因此，探索最佳干预时间和重复治疗策略至关重要。

5 总结和展望

近年来，UTMD技术作为一种新型治疗手段，因其可瞬时、可逆地打开BBB从而增加药物透过浓度，具有靶向性强、安全性高、高效能载药以及低成本等优势，在AD、PD、ALS等神经退行性疾病治疗领域展现出广阔的应用前景。

UTMD技术应用于神经退行性疾病的临床治疗面临着如下诸多挑战：a. 早期研究主要聚焦于最大化BBB开放效率，但在精准匹配个体化药物递送需求方面存在不足[97]；b. 延长超声作用时间虽可提升治疗效果，但伴随产生的热效应可能导致靶区细胞凝固性坏死及周围组织损伤[98]；c. 颅骨对超声波的衰减效应会影响超声能量传递的准确性，亟需开发新型计算模型以校正不同个体颅骨厚度和结构差异带来的影响[99]；d. 微泡的尺寸、外壳成分和气核组成等参数与BBB开放程度及恢复时间密切相关，优化微泡特性以提升药物递送效率面临复杂的调控挑战[100]，具备温度/pH响应特性的智能微泡系统虽能提升靶向精准度，但环境响应阈值的精确设定需突破技术壁垒、多参数耦合调控策略的有效构建存在较高技术难度，以及体内实时监测技术的成熟度不足，难以实现治疗进程的动态反馈与调整；e. UTMD短期应用相对安全，但长期、反复应用对BBB完整性、脑组织微结构、神经功能以及潜在免疫反应的影响，仍需通过系统、严谨的临床试验进行全面评估[101]。

综上所述，UTMD技术为神经退行性疾病的治疗带来了前所未有的机遇。随着研究的不断深入和技术的日趋成熟，UTMD技术与放疗、化疗、免疫疗法等传统治疗手段的联合应用有望成为未来研究的热点，此外，NDs病理机制复杂，且单一疗法效果有限，未来UTMD技术可构建多功能载体平台，为全球数百万患者带来希望。

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Ultrasound-targeted Microbubbles Destruction: a New Approach to The Treatment of Neurodegenerative Diseases*

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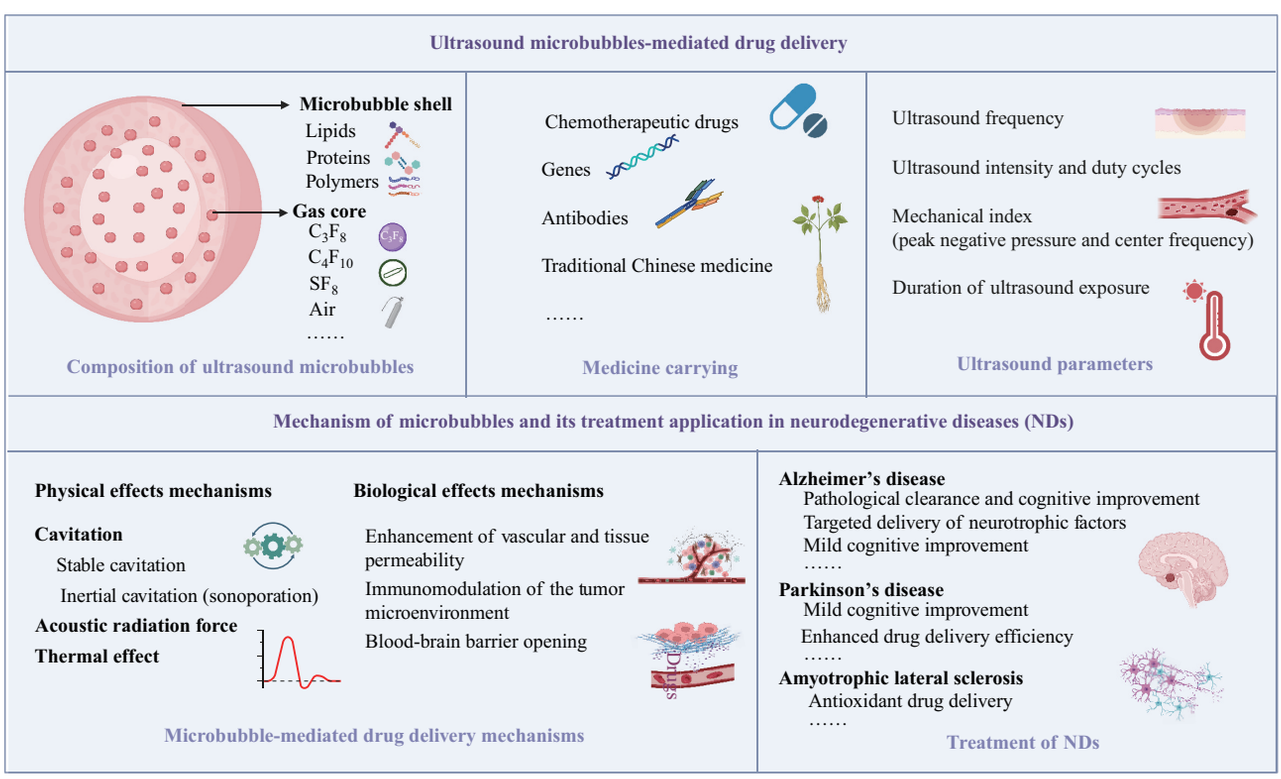
Graphical abstract



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Abstract Neurodegenerative diseases (NDs) are a group of disorders characterized by the progressive loss of neuronal structure and function, leading to clinical manifestations such as cognitive decline, motor dysfunction, and neuropsychiatric abnormalities. NDs encompass a range of conditions, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), *etc*. With the intensifying trends of global population growth and aging, the incidence of NDs continues to rise, yet no curative treatments are currently available. The blood-brain barrier (BBB) plays a crucial role in maintaining central nervous system (CNS) homeostasis by blocking harmful substances in the bloodstream from entering brain tissue. More than 98% of small-molecule drugs and nearly 100% of large-molecule therapeutics fail to cross the BBB and reach brain parenchyma. Ultrasound-targeted microbubble destruction (UTMD) is an emerging interdisciplinary technology integrating materials science and bioengineering, which combines the advantages of microbubble carriers with the physical properties of ultrasound. This innovative approach enables transient and reversible opening of the BBB, and enhancing drug delivery efficiency. Microbubbles (MB) are the core component of the UTMD system, consisting of two fundamental structural elements: a gaseous core and a biocompatible outer shell. The drug-loading capacity of MB has been significantly expanded, evolving from traditional chemotherapeutic agents to encompass nucleic acid drugs, macromolecular antibodies, and even traditional Chinese medicines. Concurrently, their drug-loading strategies have advanced from initial passive physical adsorption to active targeted delivery. UTMD possesses the following 4 biological advantages. (1) UTMD can transiently and reversibly enhance the permeability of cell membranes and blood vessels. The biocompatible shells commonly used in microbubbles can be metabolized by the body, posing no risk of long-term accumulation. (2) UTMD not only significantly improves drug delivery efficiency but also simultaneously serves as an ultrasound contrast agent and therapeutic carrier, achieving the integration of diagnosis and treatment. (3) UTMD technology offers dual advantages of spatial targeting and molecular targeting, allowing for precise drug delivery. (4) UTMD only requires conventional ultrasound equipment, and the raw materials for microbubble preparation are readily available with simple synthesis processes. Whether applied in diagnostics or treatment, the cost remains relatively low. The mechanism by which UTMD opens the BBB is primarily associated with cavitation effect and sonoporation effect. The cavitation effect induces mechanical stretching of both cellular membranes and capillary walls, creating transient, reversible channels that facilitate macromolecular drug passage, to enhance BBB permeability. Meanwhile, the sonoporation effect promotes drug penetration through dual mechanisms: (1) augmenting passive diffusion across biological barriers; (2) potentiating active transport processes. This synergistic action significantly elevates both local drug concentrations and therapeutic efficacy at target sites. The permeability of BBB is predominantly influenced by both microbubble characteristics and ultrasound parameters. Microbubble characteristics and ultrasound parameters are key factors affecting BBB permeability. By adjusting the composition of microbubbles and optimizing ultrasound parameters, effective BBB opening can be achieved while minimizing tissue damage, to regulate the dosage of drugs delivered to the brain parenchyma. Both preclinical investigations and clinical trials have consistently shown that UTMD holds significant therapeutic promise for NDs. This article outlines the fundamental properties of microbubbles and elucidates the potential mechanisms underlying UTMD mediated BBB opening. Furthermore, it systematically reviews recent advances in UTMD technology for the treatment of treating various NDs, aiming to provide a theoretical foundation and future directions for developing novel therapeutic strategies and drugs for NDs.

Key words neurodegenerative disease, ultrasound-targeted microbubble destruction, blood-brain barrier, drug delivery, treatment

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