

音乐在药物递送中的应用及研究进展

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【摘要】目前, 声音对人体生理功能的影响及其机制越来越受到关注, 音乐在辅助治疗方面也已有了一定应用基础。而在相关治疗中, 往往还会涉及药物干预; 同时, 因其他原因使用药物的人群也不可避免地暴露在各种声音环境中。基于声音对人体内分泌与免疫, 以及血流特性、吸收屏障等生理功能的影响, 其对药物在体内的吸收、分布、代谢等情况以及最终的药物疗效有潜在的作用。然而, 当前声音或音乐与药物递送相关的讨论仍相对较少, 对于其中可利用的机制和可能的风险, 均缺少关注。基于此, 本文试针对音乐对药物递送的影响及相关研究进展进行浅述。

【关键词】声音; 音乐; 药物递送

【收稿日期】2023 年 8 月 7 日 **【出刊日期】**2023 年 9 月 12 日 **【DOI】**10.12208/j.jmbr.20230005

Application and research progress of music in drug delivery

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【Abstract】Currently, growing attention has been paid on the influence of sound on human physiological functions and the related mechanisms, and music therapies have also seen applications in many situations. Drug intervention, however, is often involved in these related treatments; meanwhile, people receiving medication are inevitably exposed to various kinds of sounds in their daily lives. Based on the impact of sound on human endocrine and immune systems, as well as physiological functions including blood flow characteristics and absorption barrier functions, sound has a potential role in the absorption, distribution, metabolism of drug and its final therapeutic outcome. However, the discussion of sound or music in relation to drug delivery is still lacking, especially the potential mechanisms to be utilized and possible risks involved. In this paper, the influence of music on drug delivery and related research progress will be briefly discussed.

【Keywords】Sound; Music; Drug delivery

1 绪论

大量研究报道声音可对人体的多种生理功能产生影响, 因此在辅助治疗方面显示出一定潜力, 例如对抑郁症^[1]、自闭症^[2]、痴呆^[3]等疾病的辅助治疗, 协助改善认知和运动障碍^[4]的应用等。《柳叶刀》杂志报道了声音对于减轻术后疼痛和焦虑感、协助术后恢复等方面的作用^[5], 《科学》杂志上的最新

研究也进一步报道了声音通过皮质丘脑神经环路降低痛觉的生理机制^[6]。除此之外, 声音对血流动力学、血脑屏障等方面的影响还提示声音具备改变药物递送的效果以及最终的治疗效果的潜力。同时, 特定的药物递送系统也会受到声音的影响。基于声音对递药系统自身和药物递送过程中相关生理功能两者的影响, 声音在改变药物递送过程和药物体内

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行为的方面已显示出良好的研究价值。

声音从频率上通常可分为人耳能听到的声音信号、超声以及次声, 其中人耳可听到的声音信号又常按发声体是否作规则振动分为乐音与噪音, 音乐则是对乐音、噪音等进行组织而形成的。由于次声对人体存在一定安全隐患, 因此本文暂不展开讨论^[7,8]。目前, 超声在药物递送领域的应用十分广泛, 已有大量研究报道了超声介导的药物递送策略、诊疗一体化策略^[9,10]等等。超声一方面可通过空化作用等机制对多种递药屏障产生瞬时的影响, 从而提高药物递送效率, 例如聚焦超声(focused ultrasound, FUS)激活微泡能够可逆地打开血脑屏障并有效协助药物到达脑部^[11-13], 亦有研究报道聚焦超声能降低血脑屏障中P-糖蛋白的表达^[14]; 又如超声能够促进美沙拉嗪、胰岛素等多种药物在胃肠道中的吸收, 不仅有助于提高全身给药的口服生物利用度, 还能提高对结直肠等部位局部给药的递送效率和治疗效果^[15,16]; 除口服和注射给药外, 超声也是介导经皮药物递送的重要策略之一, 通过超声促渗作用能有效增加角质层屏障的渗透性, 提高药物的透皮吸收, 在蛋白质、核酸等生物大分子药物的递送中尤其受到关注^[17,18]; 同时, 超声还能在细胞水平上促进药物穿过细胞膜屏障入胞, 结合其对肿瘤微环境和免疫等方面的作用以及超声成像、超声消融等功能, 在抗肿瘤递药和治疗中有大量研究^[19-24]。另一方面, 超声亦可激活响应性递药系统, 例如介导微泡等递药系统破裂释放药物^[25,26], 介导微泡-纳米颗粒的转换实现多级递药^[25,27], 或通过热效应使热敏递药系统释药^[26,28], 等等; 亦有研究报道超声能直接活化药物, 如通过机械力使化学键断裂并介导前药活化^[29]、调控蛋白质和DNA结构转变^[30,31], 等等。另外, 声动力治疗^[32-34]、光声成像^[35,36]等策略的发展也进一步拓宽了超声在药物递送中的应用范围。

目前, 已有大量综述对超声在药物递送中的应用进行全面而深入地探讨, 因此本文不作赘述。音乐作为辅助治疗手段已有一定应用基础, 在药物递送相关领域中亦存在一定潜力, 然而与超声相比, 相关研究相对较少, 讨论亦不多。本文将对现有涉及音乐与药物递送相关的研究进行粗浅的、不全面地总结, 以期探讨二者可能的联系, 并为未来的相关探索提供一定参考。

2 音乐影响药物递送的可能性及其潜在机制

基于音乐对人体内分泌与免疫, 以及血流特性、吸收屏障等生理功能的影响, 本文主要从上述三个方面讨论音乐对药物递送产生影响的可能性, 并对潜在的机制进行概括探讨。

2.1 音乐对内分泌与免疫的影响

多项研究表明音乐治疗有降低患者术后皮质醇水平、肾上腺素水平等的潜力^[37-39]。Hou等^[40]在血液透析患者中的研究发现, 为期1周的音乐治疗使患者的唾液皮质醇水平显著降低并减轻了不良反应, 且唾液皮质醇的变化与呼吸频率的降低等指标正相关。Levitin等^[41]总结了三十余项有关音乐对下丘脑-垂体-肾上腺轴影响的研究, 认为上述作用与音乐风格及人格特质等相关, 在多数研究中慢节奏、低音高且无歌词的“放松型”音乐能降低皮质醇水平, 达到缓解压力、改善术后疼痛等目的, 而节奏通常较快的techno电子舞曲反而引起皮质醇水平升高。皮质醇和肾上腺素等均是压力评估时常用的指标, 同时也会对消化系统、免疫系统等的功能造成影响, 例如胃肠道蠕动和吸收速度等, 提示不同特性的音乐对药物口服吸收等过程造成不同影响的可能性。

另外, 还有多项研究报道音乐对IL-6等炎症因子^[42,43]、IgA^[37]的水平等有关。Fancourt等^[44]总结了十三项有关音乐对IgA影响的研究, 并指出受试者主动地参与音乐活动时IgA水平升高最显著。IgA可分为血清型和分泌型, 亦有部分研究报道音乐对血清型IgA的水平无明显影响^[37], 提示在后续相关研究中, 音乐刺激的选择及对对照条件的设置的标准化性至关重要。近期发表在《自然》等杂志上的多项研究报道了分泌型IgA可与肠道菌群互作并影响肠上皮细胞代谢和吸收功能^[45,46], 音乐对分泌性IgA水平及后续肠道屏障和吸收功能的具体影响, 值得进一步探究。

内分泌和免疫是对后续多种生理功能造成影响的基础之一, 影响范围也包括后文将讨论的血流特性、递送屏障等方面, 为集中叙述, 此处将其独立成段, 且只讨论了与主题较为相关、较有代表性的方面。此外, 基于音乐对炎症因子和免疫反应的影响, Freire-Garabal等^[47]还研究了其对肿瘤治疗及相关免疫功能的作用, 本文不作赘述。

2.2 音乐对血流特性的影响

在全身给药中, 药物递送系统往往需要进入血液循环并到达药物的作用部位, 其递送效果易受到相关因素的影响。Shen 等^[48]在抗肿瘤药物递送的“CAPIR”级联过程中即强调了纳米药物在血液循环系统中行为的重要性。部分递药系统的靶标就在血液循环中, 例如循环肿瘤细胞、巨噬细胞等, 递药系统与靶标进行粘附的过程即需克服血流动力学的影响^[49]。对于以血管壁为靶点的递药系统, 其在血管中截面的分布情况直接影响其与血管壁递药靶标接触的机会, 进而影响最终的靶向效果, 而除了递药系统的形状等性质外, 不同的血流特性亦可改变递药系统向血管壁分布的“着边”情况^[50,51]。除与血管壁的相互作用外, 着边性质同样会影响递药系统从血管孔隙处的渗出情况, 在针对肿瘤等靶标的主动靶向药物载体设计策略中也是值得考量的因素之一^[52]。Kataoka 等^[53]报道了纳米递药系统在部分肿瘤血管壁处通过“喷发(eruption)”外渗进入肿瘤的现象, 并指出对于不同的肿瘤, 流体压力对喷发速度具有不同程度的影响。另外, 目标部位的血流灌注量也是影响药物靶向递送效率的基础因素之一, 许多研究报道增加目标部位(如脑^[54]、肿瘤^[55]等)的血流灌注量有助于增强靶向效果。

上述多项研究均强调了血流特性在药物递送中的重要性。相应地, 已有许多文献报道了音乐对血液循环中心率、血压、血流量等相关特性的影响, 这些影响在药物递送系统的设计和不同给药途径药物的临床应用中值得关注。

Bernardi 等^[56]调查了健康的音乐家和非音乐家对六种音乐的反应, 与基线相比, 随着节奏的加快、节奏型的简化, 分钟通气量、血压、心率和大脑中动脉流量均有一定增加, 而血压、分钟通气量和心率在时长为两分钟的无声音暂停期中下降, 提示节奏对相关特性的诱导作用。Mir 等人^[57]亦报道“放松型音乐”可以降低处于高血压前期的年轻男性的收缩压和心率, 然而对该类音乐的界定标准尚未提出建议。Valenti 等^[58]进一步研究了音乐对自主神经系统的影响, 结果提示重金属音乐降低了心脏交感神经和副交感神经调节, 而巴洛克音乐降低了交感神经调节, 不同风格的音乐对心率变异性的影响不同。

Evers^[59]等采用经颅多普勒超声评估了音乐感

知时脑血流速度的变化, 研究发现非音乐家在和声感知时大脑右半球脑血流速度显著增加, 节奏感知时倾向较不明显; 而在所有的被试群体中, 语言感知都被侧向化到左半球。Meyer 等^[60]认为音乐训练经历会改变音乐感知过程中脑血流速度的变化, 同时还指出经颅多普勒超声这一方法能提供的空间信息较为有限。在相关研究中, 不同区域血流速度变化的程度是否足以在脑部药物递送中起到显著作用, 尚无明确研究证据。

2.3 音乐对药物递送屏障的影响

在不同给药途径中, 药物往往需要克服不同的生理屏障以到达作用部位, 例如血脑屏障、口服吸收屏障等, 若对上述递送屏障造成影响, 将对药物的吸收程度或作用部位的药物量产生较大改变。音乐如能在不显著或长期影响递药屏障正常生理活动的同时提高药物跨越递药屏障的能力, 则可协助药物更好地达到作用部位发挥药效。另一方面, 如因为音乐意外改变了递药屏障的性质, 则会造成药量失控的风险。

血脑屏障是最受关注的递药屏障之一, 如何有效跨越血脑屏障是药物脑部递送的重要课题。Semyachkina-Glushkovskaya 等^[61]发现音乐能诱导健康小鼠血脑屏障的可逆性开放。研究使小鼠持续 2 小时暴露在音乐中(90-100 dB, 11-10000 Hz), 暴露后 1 小时血脑屏障出现延迟性开放, 增加了较高分子量(70kDa)和较低分子量(928Da)物质跨越血脑屏障入脑的程度。该研究认为音量较大的音乐可造成肾上腺素升高、脑血流量上升、脑血管张力改变, 并造成 claudin-5 等紧密连接蛋白降低, 导致血脑屏障的短暂开放。该团队后续在脑胶质瘤小鼠模型上验证了该现象, 音乐诱导(Music)有效增加了贝伐单抗(BZM)在脑内的分布, 经治疗后 BZM+Music 组肿瘤体积($64.1 \pm 3.3 \text{ mm}^3$)比 BZM 组($111.3 \pm 9.2 \text{ mm}^3$)显著更低, 表现出更好的抑瘤作用^[62]。作者指出, 音量较大的音乐会对小鼠造成较大压力, 但作用于人体时还需考虑其他的、不同的影响因素。另外, 该研究中肿瘤模型的初始体积较小, 而不同种类、大小的肿瘤中血管生长情况各异, 音乐诱导在上述不同情况下的作用还有待更多研究。

口服给药是应用最广泛的给药途径之一, 胃肠

道的生理功能直接影响药物的口服吸收情况^[63]。研究报道音乐有增加健康成人胃肌电活动振幅, 从而促进胃运动增加, 刺激胃排空的潜力^[64]。在报告实验使用的音乐令人愉快的被试中, 音乐对胃电的作用与 5-羟色胺 4 受体激动剂的效果类似。Chen 等^[65]进一步研究了不同年龄和是否禁食的情况下, 音乐对胃活动的影响, 结果提示禁食状态下青少年的胃慢波、交感神经迷走神经平衡性等较成年人更容易受到音乐的影响。另外, 研究表明音乐可诱导分钟通气量改变^[66], 而深呼吸可激活迷走神经并进一步改善胃肠道运动情况^[67], 因此音乐亦有从该机制进一步影响药物口服吸收的可能性。Zhao 等还报道^[68], 在喂食小鼠的同时使用音乐干预提高了小鼠肠道中乳杆菌等的丰度, 同时降低了变形菌等的丰度, 上述肠道菌群的变化也提示音乐对口服药物吸收、代谢和生物利用度等产生影响的可能性^[69]。

3 总结与展望

音乐对人体的影响较为复杂, 且受影响因素较多、个体差异大, 因此其确切的机制研究相对比较困难, 也对后续的研究及应用造成了一定难度。除实验中常包含的变量外, 人格特质、压力水平、睡眠习惯等等, 在实验中均可能对结果造成干扰, 影响其可靠程度^[70]。另外, 听力环境、一天中的时间和对音乐的偏好及熟悉程度等等亦可能会影响音乐对生理功能的作用^[71]。Vuust 等^[72]在 *Nat Rev Neurosci* 上发表的最新综述强调了预测在个体的音乐感知及后续反应中的重要性, 并对音乐的预测编码模型 (predictive coding of music, PCM) 进行了系统阐释, 对相关研究中的个体差异提供了解释。该报道认为, 预测行为是大脑进行信息处理和后续反应的基础之一, 音乐对人体生理反应的影响情况不仅与听觉相关, 还与个体对音乐的预测模型紧密相关。预测模型受个体长期的适应和学习经历、对某种音乐体裁或音乐作品的熟悉程度、以及短期内的音乐聆听经历等各种因素的影响。而主动聆听的过程是人体对音乐产生反应的基础, 同时个体也会在该过程中不断建立和更新自身的预测模型, 对接下来的音乐进行预测。现有的许多实验中, 难以对个体的预测模型进行控制, 亦难以确保个体是否主动地进行音乐聆听活动, 因此部分研究中尝试使用了这种方案, 让被试者自主选择要聆听的音乐, 或以

个体对音乐的“喜好”为衡量指标之一进行讨论。随着相关领域基础研究的不断推进, 有望对上述困难提出更好的解决方案, 同时为治疗和递药方面的后续应用提供更坚实的理论依据与研究基础。

音乐主要包括旋律、和声和节奏等要素, 三者涉及的神经网络有一定重叠, 但不完全相同^[72], 许多机制研究按上述三要素进行分类讨论, 该模式对应用于研究中音乐刺激与实验对照的选择有一定参考意义。同时, 目前神经科学领域对于相关问题的研究更多侧重于西方音乐^[72], 在音乐对人体生理功能影响的研究中亦是如此。对于其他地区和文化中的音乐, 例如中国传统音乐, 虽自《黄帝内经》起便有五音疗疾等思想, 但其神经科学层面的机制研究、及与药物递送相关的可能应用和研究仍有待进一步阐明。另外, 研究报道人类对音乐产生反应的常见机制包括受后天学习影响较小的固有反应, 与视觉想象、情景记忆等相关的音乐外联想, 以及与文化、训练等密切相关的心理预期等^[73]。相应地, 对于更具共性或更具个性的研究对象, 研究中可重点关注的机制并不相同, 在偏重针对群体或偏重针对个体的治疗与药物递送研究中, 更值得关注的机制可能分别倾向于较有普适性的固有反应机制, 和较为个性化的心理预期等机制。

随着机制研究的不断深入, 音乐作为辅助治疗手段的应用正在不断发展^[74,75], 音乐对药物递送产生的影响也值得进一步关注, 以发掘通过音乐对药物递送进行调控、使药物更好地发挥作用从而优化治疗效果的可能性。另一方面, 由于人们用耳习惯的改变, 以及有较大音量的活动场所的不断增加等原因, 世界卫生组织近年已对各类声音造成的听力丧失风险进行了反复警示, 据估计至 2050 年听力丧失将影响全球四分之一的人口, 带来严重的社会负担。而站在药物递送的角度, 人们在上述环境条件下不仅需要注意听力下降等症状, 还有必要研究环境中的声音对所服药物的体内递送情况和最终治疗效果的影响, 以对潜在的风险有更清晰的认知和把握。

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