·综述·

经颅直流电刺激在肥胖治疗中的应用进展*

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1 肥胖的流行病学

肥胖已逐渐成为全球关注的公共卫生问题。WHO规定,对于成年人,超重是指体质指数(body mass index,BMI)≥25,BMI≥30即为肥胖。从1975—2014年,在全球200多个国家中,男性肥胖者的比例从3.2%增长到10.8%,女性肥胖者的比例从6.4%增长到14.9%,并且仍然呈上升趋势。到2025年,全球男性肥胖的比例有望达到18%,女性将超过21%[1]。在我国,肥胖同样也是一个不容忽视的健康问题。2012年,我国成年人中超重和肥胖者的比例占42%,儿童中超重和肥胖者的比例为16%[2]。研究表明,肥胖患者发生糖尿病、心血管疾病、恶性肿瘤等疾病的风险明显高于正常人[3]。中年人超重和肥胖均会增加死亡的风险[4]。所以,帮助肥胖患者减重所带来的效果并不仅仅是体重的减轻,更是促进其身体健康的一项重要措施。肥胖的病因复杂,与遗传、社会经济和文化因素均有相关性[5],因此,对于不同的减肥方式,个体间的差异性较大。通过改变生活方式,包括减少食物的摄入及增强运动来增加能量的消耗等仍然是最基本和常见的减肥方式,但是只有大约20%的人能够长期坚持,大多数人往往因为难以坚持而无法达到预定的目标[6]。此外,常用的减重方法还包括药物治疗和外科手术干预[7—8]。药物治疗因其较大的副作用多不被推荐使用[8]。通过外科减重手术可以有效地减轻肥胖者的体重[9],但是其中大约20%—30%的人减重效果不理想[10],一部分人体重会出现反弹[11],而且可能会合并一些手术相关的并发症,风险较高[12]。因此,目前的减肥方法尚不能完全满足临床的需求。

2 tDCS的概述

tDCS是一种非侵入性的大脑皮层调控方法,它通过放置在头皮上的一个或两个电极,向头皮施加微弱的直流电[13],可以诱导神经可塑性改变和调节大脑皮层的功能[14]。阳极刺激通过引起神经元去极化,进一步提高大脑皮层的兴奋性,阴极刺激则使神经元超极化,进一步导致大脑皮层兴奋性降低[15]。与重复经颅磁刺激(repeated transcranial magnetic stimulation,rTMS)相比,tDCS更加安全(癫痫发作的风险较低)、便宜、便携,耐受性良好[16—17],而且其对大脑皮层功能的调节持续时间更长[17]。随着神经科学的发展,目前tDCS已应用于诸多领域,比如:药物成瘾[18]、卒中[19]、癫痫[20]、帕金森病[21]、阿尔茨海默症[22]和抑郁[23]。tDCS正逐渐受到越来越多人的关注,未来将会应用到更广泛的研究领域中。

3 tDCS治疗肥胖的机制

有研究表明,与正常人相比,肥胖患者纹状体中多巴胺D2受体数量减少,而且多巴胺D2受体的数量与肥胖患者的BMI值成反比[24]。通过使用抗精神病药物阻断多巴胺D2受体,可以进一步增加食物的摄入量,从而使发生肥胖的风险升高[25]。另有动物试验研究表明,肥胖小鼠多巴胺D2受体数量的减少,会导致其产生强制进食的行为[26]。从以上研究中,我们可以发现多巴胺D2受体数量的减少与肥胖发生有一定的相关性。此外,有研究发现,肥胖患者多巴胺D2受体数量的减少,与大脑前额叶皮层区域(背外侧前额叶皮层,眶额内侧皮层,前扣带回)的代谢活性降低[27]和功能失调相关[28]。前额叶皮层活动较少的人更容易暴饮暴食,尤其是在受到诸如食物广告之类的提示时,从而导致体重的增加和肥胖[29]。

此外,执行功能(即更高层次的认知加工)的损害与肥胖也有一定的相关性,其中包括:认知灵活性,处理速度和决策能力[30]。执行功能差的人更容易摄入含更多卡路里的食物[31—34]。神经影像学研究发现,前额叶皮层是调节执行功能的关键脑区[35—37]。其中背外侧前额叶皮层(dorsolateral lateral prefrontal cortex, DLPFC)主要负责高级的认知功能,比如:对饮食的认知控制,奖励评估,工作记忆和注意力的维持,及运动计划[38—39]。与体型偏瘦的人相比,肥胖患者餐后大脑DLPFC区域活性较低[40—41]。然而在肥胖患者成功减重后,大脑DLPFC区域活性可再次升高[41]。DLPFC区域的活性下降与控制饮食的能力降低有关,尤其是在肥胖的人群中[42—43]。使用tDCS刺激DLPFC区域对应部位的头皮,可能激活该区域的大脑皮层,进一步调整进食行为,从而达到减重的效果。

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4 检索方法及纳入与排除标准

4.1 检索方法

本文检索了PubMed数据库，未设定时间限制，检索词：("Transcranial Direct Current Stimulation"[Mesh]) OR (tDCS[Title/Abstract])) OR (Cathodal Stimulation Transcranial Direct Current Stimulation[Title/Abstract])) OR (Cathodal Stimulation tDCS[Title/Abstract])) OR (Cathodal Stimulation tDCSs[Title/Abstract])) OR (Stimulation tDCS, Cathodal[Title/Abstract])) OR (Stimulation tDCSs, Cathodal [Title/Abstract]))) OR (tDCS, Cathodal Stimulation[Title/Abstract])) OR (tDCSs, Cathodal Stimulation[Title/Abstract])) OR (Transcranial Random Noise Stimulation[Title/Abstract])) OR (Transcranial Alternating Current Stimulation[Title/Abstract])) OR (Transcranial Electrical Stimulation [Title/Abstract])) OR (Electrical Stimulation, Transcranial [Title/Abstract]))OR (Electrical Stimulations, Transcranial [Title/Abstract])) OR (Stimulation,Transcranial Electrical[Title/Abstract])) OR (Stimulations, Transcranial Electrical[Title/Abstract])) OR (Transcranial Electrical Stimulations[Title/Abstract])) OR (Anodal Stimulation Transcranial Direct Current Stimulation[Title/Abstract])) OR (Anodal Stimulation tDCS[Title/Abstract])) OR (Anodal Stimulation tDCSs [Title/Abstract])) OR (Stimulation tDCS, Anodal[Title/Abstract])) OR (Stimulation tDCSs, Anodal[Title/Abstract])) OR (tDCS, Anodal Stimulation[Title/Abstract])) OR (tDCSs, Anodal Stimulation[Title/Abstract])) OR (Repetitive Transcranial Electrical Stimulation[Title/Abstract])) AND (obesity)

4.2 纳入标准

①随机对照临床研究；②研究对象为健康的超重和肥胖人群；③干预措施为tDCS；④观察指标为体重、食物渴求或食物摄入。

4.3 排除标准

①动物实验研究；②研究对象为暴食症、Prader—Willi综合征（PWS）及病态肥胖合并代谢综合征的人群；③采用除tDCS之外的其他神经调制方法；④观察指标与体重、饮食行为无关。

5 tDCS对于肥胖的治疗效果评估

5.1 体重

Marci等[44]进行了一项随机对照试验，将tDCS电流强度设置为2mA，刺激左侧DLPFC区域，单次刺激40min，共刺激6次，结果发现，通过tDCS激活左侧DLPFC皮层的兴奋性，能够有效降低单纯性肥胖患者的体重。而Priscila等[45]的研究结果与之相反，在单纯性肥胖的健康女性中tDCS同样作用于左侧DLPFC区域，采用2mA的电流，单次刺激时间设置为30min，共干预10次，结果发现tDCS不仅不能有效的降低体重，而且在6个月后的随访过程中发现，与对照组相比，tDCS干预组体重反而升高。通过对参与者的基因型进行分析发现，经过tDCS刺激后体重升高的这种现象仅发生在COMT Val158Met基因非携带者中。有研究进一步证实，tDCS的作用效果与个体的基因型相关，对于COMT Met基因携带者，tDCS能够更有效地降低饥饿感、食欲和食物消耗量[46]。Carlos等[47]采用2mA的电流强度刺激大脑左侧DLPFC区域，在第1周，单独使用tDCS刺激，刺激时间为20min，共刺激5次，在第2周，tDCS联合低卡饮食治疗，tDCS隔天刺激1次，共刺激3次，后未再进行特殊干预，在第4周结束时，对比tDCS干预组与对照组对于超重和肥胖的健康女性的减重效果，结果发现干预组的体重减轻了2.32%，而对照组体重仅下降1.29%。Carina[48]等为明确tDCS联合低卡饮食对体重的影响，将tDCS刺激右侧DLPFC区域，每周刺激5次，连续作用4周，共20次，结果发现其降低体重的效果虽然无显著性差异，但是仍然有一定的作用效果。

5.2 食物渴求

食物渴求强烈的人更容易超重和肥胖[49]。对于通过外科手术减重的患者来说，食物渴求也可以作为一个预测体重反弹的指标[50]。因此，通过降低肥胖者的食物渴求，有望进一步达到减重的目的。Mary等[51]发现对于单纯性肥胖的患者，使用tDCS刺激左侧DLPFC，采用2mA的直流电，刺激时间为20min，能够降低其食物渴求能力。Maria等[52]将tDCS作用于食物渴求强烈的健康女性，刺激部位为右侧DLPFC区域，电流强度设置为2mA，刺激20min，结果发现单次tDCS刺激能够降低即刻的食物渴求，尤其是对于甜食的食物渴求能力下降更加明显。Ljubisavljevic等[53]对正常体重和超重的食物渴求强烈的健康年轻人群，采用2mA的直流电，刺激右侧DLPFC，连续刺激20min，重复刺激5天，发现食物渴求降低持续的时间至少可以达30天。

但是，Claudio等[54]的试验发现经tDCS刺激大脑右侧DLPFC区域后，食物渴求能力并没有出现下降，推测一方面可能与受试对象相关，该试验的研究对象是健康正常体重的女性，未提前对其食物渴求进行评估筛选，另一方面可能与本实验中tDCS设置的电流强度为1mA有关。Marron等[55]为了明确前额—小脑径路对食欲的调节作用，将tDCS阳极放在左侧的DLPFC区域，阴极放在肥胖患者右侧的小脑，同时设置对照组进行对比，结果发现tDCS干预后受试者的食物渴求和饥饿感反而增加，推测可能原因为tDCS阴极对小脑的抑制效果强于其阳极对DLPFC的激活效果。Ray等[56]为了进一步明确，tDCS降低食物渴求的作用效果是否与个

体对tDCS的期待效应有关,进行了一项随机对照试验,将tDCS能够降低食物渴求这一作用效果,提前告知所有受试的超重和肥胖的健康成年人,使个体对tDCS的作用效果产生一个期待效应,其中50%的人被告知接受的是真实的tDCS刺激,另外50%的人被告知接受的是伪刺激,而实际情况是在以上的两组中,每组均各有一半的人接受真实的tDCS刺激,另一半人接受伪刺激,结果发现,单纯使用tDCS并没有降低食物渴求,而对tDCS有期待效应的个体其食物渴求出现了下降。未来仍需要更多的研究进一步明确tDCS对食物渴求的作用效果。

5.3 食物摄入

Grundeis等[57]使用单次tDCS作用于肥胖的健康女性,电流刺激强度为2mA,刺激时间为20min,刺激部位选择为大脑左侧DLPFC区域,结果发现其食物摄入量并没有出现减少。Heinitz等[58]研究发现,与对照组相比,tDCS采用2mA的电流强度,单次刺激40min,短期tDCS刺激(3次)大脑左侧的DLPFC区域,不能降低健康肥胖者的食物摄入和体重,而长期tDCS刺激(15次)能够有效降低食物的摄入和饥饿感。

6 tDCS的安全性

Carlos等[47]研究发现,tDCS采用2mA的电流,连续刺激20min后,受试者耐受性良好,没有发现严重的不良反应,干预组刺激部位皮肤发红的发生率为75%,而对照组的发生率为44.4%。Heinitz等[58]进行的一项随机对照试验,tDCS同样是设置为2mA的电流,作用时间延长至40min,结果表明,与对照组相比,干预组皮肤发红的发生率高于对照组,而在头痛、颈痛、头皮烧灼感、刺痛感、情绪改变、睡眠等方面的发生率与对照组相比没有统计学差异。有报道指出[59],tDCS刺激部位皮肤轻微发红并不一定是皮肤损伤的表现,很可能是由于血管扩张引起的。一项纳入了1000人(包括正常健康人群,弱势群体及患者)的系统回顾[60],分析表明tDCS(≤40min,≤4mA)作用上述人群不会产生严重的不良反应或不可逆损伤。由此可见,tDCS作为一种非侵入性的大脑刺激技术,使用起来相对安全。

7 展望和局限性

随着肥胖的人群在全球所占的比重越来越多,有关肥胖减重的研究也在逐渐增多。在临床方面,肥胖是发生糖尿病、心脑血管等疾病的危险因素,积极控制体重有助于减缓原发病的进展,但是在上述人群中,大多不耐受剧烈运动、节食、药物及外科手术来进行减重,因此,tDCS作为一种非侵入性脑刺激技术,通过调节个体的进食行为,有望使肥胖患者体重减轻,具有良好的发展前景。同时,对于外科减重的患者,可以尝试联合应用tDCS,有望观察到更为明显的减重效果。但目前仍有以下问题需要解决:①目前的临床试验样本量较小,缺乏大样本的随机对照试验;②对于tDCS的最佳刺激参数,目前尚无统一的标准,大多数试验采用的tDCS电流强度为2mA,单次持续刺激20min,最佳刺激部位(左侧的DLPFC或右侧的DLPFC)以及最佳的刺激次数仍需要更多的试验来进行明确;③关于tDCS的长期治疗效果,相关的临床研究较少;④目前部分研究将tDCS与节食结合起来,可以观察到更为显著的减重效果,但是tDCS是作为独立的还是辅助的治疗方式,尚需进一步的探索。因此未来的研究还需选用更具代表性的样本,延长随访时间,明确tDCS的最佳的刺激参数,以达到更好的减重效果。

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