· 综述 ·

雌激素与认知障碍-痴呆症的相关研究进展

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DOI：10.3969/j.issn.1009-6574.2020.07.007

【摘要】 绝经后女性患认知障碍、阿尔茨海默病(AD)的风险会增加，而雌激素治疗具有改善认知的作用。雌激素具有明显的神经保护作用，现就雌激素如何影响认知和更严重的认知缺陷(如AD)方面的问题进行综述。

【关键词】 雌激素类； 认知障碍； 痴呆； 综述
基金项目：国家重点研发计划(2016YFC1307200)；北京市属医院科研培育计划(PX2018064)

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【Abstract】 Postmenopausal women have an increased risk of cognitive impairment-Alzheimer disease (AD), while estrogen therapy has showed contribution to the improvement of cognitive function impairment. Estrogen has significant neuroprotective effects. This article reviews how the estrogen affects cognition and more serious cognitive deficits, such as AD.

【Key words】 Estrogens; Cognitive disorders; Dementia; Review
Fund programs: National Key Research & Development Program of China (2016YFC1307200); Beijing Municipal Hospital Research and Cultivation Program (PX2018064)

阿尔茨海默病(AD)患者发病率存在一定的性别差异，女性占2/3，女性在绝经后患AD的风险增加[1-2]。与男性不同，女性进入绝经期后，卵巢等性腺器官开始萎缩，其合成分泌功能不足，导致体内雌激素水平逐渐降低，提示体内雌激素水平可能参与了AD发生发展的过程。循环中雌激素(雌二醇)的减少被认为是女性患AD风险增加的原因之一，低水平的雌激素与女性AD的病因学有关[3-5]。早期暴露于雌激素的时间越长，晚年的认知能力越好，绝经后使用雌激素治疗可增强前额叶的认知控制功能[6-7]。雌激素在大脑功能中的作用已经逐步被发现，许多高级大脑功能，如情绪、精神疾病、行为以及认知，均会受到激素的影响[8]。现就雌激素通过何种方式影响认知及AD进行讨论。

一、雌激素调节神经递质

雌激素已经被证明对大脑神经递质水平有积极的影响，大脑中雌激素受体的分布也表明，神经递质介导了雌激素的一些认知效应[9]。雌激素也是重要的神经营养因子，影响神经的发生和大脑功能的平衡，进一步强调了雌激素在神经系统中的作用[10]。雌激素通过增加海马区的脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)水平，进而增加神经的连接性和可塑性，帮助改善认知[11]。此外，雌激素能够调节乙酰胆碱能的代谢，而乙酰胆碱对注意力和记忆过程至关重要[12]。雌激素能够促进神经营养素的合成，调节胆碱能和多巴胺能神经递质系统，保护大脑免受压力和炎症的损害。雌激素对大脑的影响受到多巴胺水平的影响[13-15]。青春期的大脑是由雌激素和糖皮质激素相互作用，且通过对多巴胺类神经递质的影响而形成[15]。雌激素通过多巴胺系统调节学习机制、奖励机制、工作记忆等方面影响认知功能[16]。雌激素对工作记忆的影响取决于多巴胺的基线水平，多巴胺的个体基线水平可能对雌激素表现出不同的敏感性[17-18]。与既往研究一致，

多巴胺驱动的认知功能(如工作记忆和反应抑制)存在性别差异,该差异受雌激素的影响明显[16, 19]。由此可见,雌激素可以通过与BDNF、乙酰胆碱、多巴胺等多种神经递质的相互作用进而影响认知功能。

二、雌激素影响代谢和抗氧化

雌激素通过提高抗氧化剂的水平,减少自由基的生成,并大幅降低线粒体DNA的氧化损伤,调节葡萄糖和氧化代谢、线粒体功能中三磷酸腺苷的合成,提高对钙内流的耐受性和触发抗氧化作用来保护细胞,上述过程的变化是延缓神经退行性疾病(如AD)进展的主要特征[20-21]。雌激素已被证明在调节大脑中的葡萄糖代谢中起关键作用,葡萄糖代谢与认知能力的提高密切相关,因此,低水平的雌激素导致的大脑葡萄糖供应和摄取的减少可能部分解释了绝经后认知能力改变的原因[22]。由此可见,雌激素的多种神经保护功能与其抗氧化、抗感染和减少缺血性损伤等特点相关。

三、雌激素促进脑区树突棘的生长

众所周知,海马脑区与认知功能密切相关,脑区部位的突触是神经元之间进行联系、生理活动的关键性结构,是信息储存和传递的基本单位,与认知活动密切相关。记忆功能的下降与海马树突棘的减少有关[23]。动物研究表明,低水平的雌激素会对神经元产生直接影响,导致突触丢失和连接性降低[24]。卵巢切除术后认知功能的下降,可能与脊髓神经元密度显著降低相关[25]。高水平的内源性雌激素与女性海马区体积的增大相关[26]。研究证实雌激素对海马突触的可塑性和海马介导的认知行为具有强大的作用,雌激素受体可能介导了雌激素对海马突触可塑性的影响[10, 27]。卵巢切除的雌性老鼠,海马区的突触蛋白磷酸纳蛋白酶和突触素水平明显降低,雌激素能够改善卵巢切除术后小鼠海马树突棘的突触形成[22, 28],获得更高水平的突触前雌激素α受体与更强的记忆能力,雌激素治疗能够促进海马和前额叶皮层表面树突棘的增长[11, 29]。近年来的研究也证实了雌激素的脑区特异性作用,进一步强调了雌激素对海马CA1区神经元形态和可塑性的强大作用[30-31]。因此,激素水平下降引起的神经保护作用减弱可能会使海马的病理生理学更易受到影响。

四、雌激素影响遗传多态性的表达

有足够的证据表明,在研究雌激素-痴呆的关系时,应该考虑遗传信息的作用。雌激素受体-1的基因多态性似乎与认知障碍的风险有关[32]。载脂蛋白e4(APOE e4)等位基因、APOE e4基因型的杂合子和纯合子携带者患AD的风险分别增加4~12倍[33]。APOE基因型引发AD的风险是由性别决定的,女性患AD的风险比男性高,女性APOE e4基因携带者患AD的风险显著增加[34-35]。有研究推测雌激素和APOE基因型可能存在相互作用,两者都参与的脂质代谢[36]。临床试验表明,激素替代治疗对认知下降的保护机制与APOE基因型存在相互作用[37-38]。具有APOE e4基因型的女性易患AD,更易受益于激素替代疗法,减缓认知功能的下降[39]。雌激素、认知障碍和遗传状态(特别是APOE基因型)之间的相互作用的研究,对认知下降、AD的高风险人群的了解至关重要,然而,雌激素与认知改变、早期AD之间的特定遗传学机制仍需进一步的研究。

五、雌激素影响炎性反应

雌激素可以通过介导免疫系统对认知产生影响。研究发现,认知障碍的机制是由于免疫系统对雌激素的下降产生反应,进而引起的脑部炎症[40]。在年龄70~90岁(假定更年期的年龄)的轻度认知障碍老年妇女中(而非男性中)发现,肿瘤坏死因子(TNF-α)含量严重超标,表明在炎症和认知障碍之间存在潜在的性别差异[41]。总体来说,卵巢切除术后内源性雌二醇的减少与周围炎性标志物的增加有关,子宫切除术后的患者C反应蛋白比对照组的女性高出3倍[42]。激素替代治疗似乎可以逆转绝经后女性体内促炎因子的增加[43]。卵巢切除后的女性和处于自然绝经期的女性均表现出系统性的炎症[44]。绝经期女性伴有雌激素水平下降时,白细胞介素-6(IL-6)、IL-1、TNF-α等炎性因子的水平显著增加[45]。炎症也参与了AD的病理生理过程,进一步表明,认知能力下降、低水平的雌激素和炎症之间存在密切的联系[46]。AD是一种炎症性神经退行性疾病,其原因与血脑屏障的破坏相关,然而雌二醇有助于维持血脑屏障的完整性[47]。上述研究均提示雌激素水平的下降可能导致炎性因子水平的升高,进而影响了认知功能,但具体的炎性指标与认知功能的关系仍需深入的研究。

六、其他方式

雌激素不仅通过上述方式影响认知功能,还存在一些其他的方式。众所周知,雌激素通过雌激素受体激活认知相关的大脑区域,如前额叶皮层和海马,进而影响认知功能[48]。脑中雌激素的活性主要通过雌激素受体介导产生,雌激素受体广泛分布于大脑中涉及情绪和认知调节的区域[49]。雌激素可以减少β-淀粉样蛋白(Aβ)在大脑中的沉积,从而对AD的病理生理过程有更直接的影响[50]。雌激素在AD中的一个重要的神经保护作用是当出现病理诱因时,雌激素可以降低Aβ的水平,或者阻止Aβ的上升[51]。雌激素也可以通过调节Bcl-2蛋白家族,

增加抗凋亡细胞Bcl-xL和Bcl-w的表达，抑制促凋亡细胞Bim的表达来防止Aβ介导的神经元损失，从而起到保护认知的作用[52]。越来越多的证据表明细胞膜信号通路的启动在雌激素介导的记忆增强中起着关键作用，包括记忆加工和社会行为[53-54]。由此可见，雌激素通过影响Aβ、膜信号通路、雌激素受体等进一步影响认知功能。

七、小结与展望

越来越多的证据表明，激素变化与认知、AD之间不仅存在相关性，而且存在因果关系，目前的研究仅能发现雌激素可能通过与多巴胺类神经递质、葡萄糖代谢抗氧化、海马区的突触棘的生长、APOE e4等位基因、炎性因子等相互作用进而影响认知功能，但具体的主流学说迄今为止在文献中还没有得到充分的阐述。未来有待进一步的研究，探索雌激素影响认知功能的途径，进而从神经因子、基因多态性、炎性因子等多维度出发，为将来雌激素的早期干预起到部分提示作用，从源头上延缓认知障碍甚至AD的发生发展，帮助减轻疾病负担。

利益冲突 文章所有作者共同认可文章无相关利益冲突

作者贡献声明 构思为汪晓、周晶晶，论文撰写为汪晓，论文修改、审校为周晶晶

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(收稿日期: 2020-06-06)
(本文编辑: 戚红丹)