· 综述 ·

早年创伤事件和端粒长度与抑郁症关系的研究进展

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【摘要】 抑郁症是严重精神疾病的一种，其机制涉及心理-生理-社会多方面，早年创伤事件导致的早年生活压力是抑郁症的主要风险因素。有研究表明抑郁症患者存在端粒缩短现象，端粒长度缩短可能与抑郁症的发生有关，特别是遭受早年创伤事件也与端粒缩短有关。现阐述早年创伤事件和端粒长度与抑郁症的关系，以及早年创伤事件影响端粒长度的相关机制，探究其中相关的病理机制，为抑郁症防治提供重要的临床参考意义。

【关键词】 抑郁症； 早年创伤事件； 端粒长度； 综述

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Advances in the relationship between early traumatic events and telomere length and depression

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【**Abstract**】 Depressive disorder is one of the serious mental diseases, and its mechanism involves psychological, physiological and social aspects. Early life stress caused by traumatic events is a major risk factor for depression. Studies have shown that patients with depression exhibit telomere shortening, which may be related to the occurrence of depression, especially with exposure to early traumatic events. This paper describes the relationship between early traumatic events and telomere length and depression, and reviews the related mechanisms of early traumatic events affecting telomere length, so as to explore the genetic and pathological mechanisms related to the two, and provide important clinical reference significance for the prevention and treatment of depression.

【**Key words**】 Depressive disorder; Early traumatic events; Telomere length; Review

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抑郁症是全球主要的公共卫生问题之一，影响全球超过2.8亿人，它是导致残疾、生活质量差和经济负担重的精神疾病[1]。既往研究表明，早年创伤事件是抑郁症的一个重要危险因素，有早年创伤事件的抑郁症患者常具有症状复杂，生活质量低的特点，其自伤自杀、代谢性疾病和心血管疾病的发生率较高，预期寿命也缩短[2]，这些风险通过生物和社会心理途径可能跨越几代人。然而，连接两者的生物学中介效应尚未完全清楚。有研究发现端粒长度与早期创伤事件是相关的表观遗传因素，尤其是与抑郁症的发生有一定关联，且童年期创伤会加速端粒缩短的进程[3]。现就早年创伤事件与端粒长度和抑郁症的交互影响及相关机制进行综述。

一、端粒长度与早年创伤事件

端粒是高度保守的核糖核蛋白复合物，覆盖在真核生物染色体上，端粒作为细胞表观遗传调节剂，保护它们免受损伤，在没有修复的情况下，会随着每次复制而缩短[3]。因此，端粒长度在出生时最长，随年龄的增长逐渐缩短，端粒长度缩短可加速细胞衰老、凋亡，并增加基因变异的可能性，是生物

学衰老的标志物[4]。有研究认为整个生命周期的逆境或应激和端粒长度与抑郁症发生相关，并认为端粒磨损是影响个体内环境稳态的生物学标志物[5]。Puterman等[6]研究了4 600多名健康男性和女性唾液中的端粒长度与童年和成年期创伤或慢性应激的关系，发现严重的经济拮据、创伤事件与唾液端粒缩短有关，生命周期的创伤累积可预测端粒缩短概率增加6%，尤其是早年创伤事件更为显著。早年创伤事件包括产前暴露于母亲的应激和童年逆境等一系列不良事件[7]。

1.产前暴露于母亲的应激与端粒长度变化：母亲怀孕期间吸烟、维生素B_{12}缺乏和有抑郁等不良情绪是导致新生儿端粒长度较短的危险因素[8]。一项前瞻性研究发现，母亲孕期应激可显著预测新生儿端粒缩短，而母亲的心理弹性与新生儿端粒长度呈正相关，良好心理弹性每增加一个标准差可预测新生儿端粒增长12%[9]。这种代际联系可能存在性别差异，与男性新生儿相比，女性新生儿的端粒长度变化更有可能受母亲端粒长度、心理健康和血浆维生素B_{12}水平的影响[8]。

2.童年逆境与端粒长度：童年逆境也称童年不良生活事件、童年不良经历、早期生活压力，包括情感虐待、躯体虐待、情感忽视、躯体忽视、性虐待、亲子分离等一系列不良经历，儿童可能同时暴露于多种逆境事件[7]。一项荟萃分析研究表明，童年经历和父母分离与端粒变化之间存在显著的关联[10]。Ridout等[11]的荟萃分析显示，早年躯体虐待和忽视经历均与较短的端粒有关，特别是性虐待与端粒长度的关联性更强[12]。端粒不仅受个体童年不良事件的影响，还受社会环境压力的影响，Theall等[13-14]在控制个体性格特征后，发现邻居暴力和居住环境混乱等也与较短的端粒相关。同时，端粒长度受逆境发生的时点影响。端粒在生命早期受损大于后期，如发生在5岁之前的不良生活事件对端粒缩短有更大的影响[15]。也有研究发现0～12岁经历的创伤与较多的白细胞端粒损耗有关[16]。此外，童年逆境对端粒长度的影响可能存在累积效应。有学者研究终生逆境对端粒的影响时，发现每发生一次童年不良事件，成年端粒较短的概率就会增加11%[6]，儿童和青少年时期经历更多的不良经历能显著预测更多的白细胞端粒损耗[17]。

总之，早年创伤事件及成年期生活事件均可能与端粒缩短有关[18]，且更多的终生应激源与更多的白细胞端粒耗损相关[16]，尤其童年期创伤影响最为显著[19]。童年期是大脑和其他生理系统发育成熟的敏感时期，在此期间，暴露于长期应激会产生持久的生物-心理学影响[7]。但也有研究发现，童年期创伤和成年期生活事件对端粒长度无明显影响[20]。这些研究的差异可能是端粒检测的方法、创伤的评估和受试者的诊断等有所不同。

二、早年创伤事件与抑郁症

抑郁症的发病机制较为复杂，主要包括遗传和环境因素。近年来，人们越来越关注童年期创伤与抑郁症之间的关联研究。从出生到6岁，大脑经历了最快速的生长和发育期[21]，所以童年期创伤可能是影响脑发育的危险因素。无论是前瞻性研究[22]还是荟萃分析[23]，均表明早年创伤事件是抑郁症发生的高危因素，儿童和青少年期经历早年创伤事件后，患抑郁症的风险比无早年创伤事件的人高5倍，前者的影响在发育早期或成年之前就出现了，且与早年创伤事件的类型有关，如家庭亲人丧失、性虐待、情感虐待与抑郁症发生的关联性更密切。研究发现经历童年期创伤的抑郁症患者发病年龄较早、病程较长、复发率高，常伴有与创伤相关的共病问题，且治疗反应率较低[24]，非自杀性自伤和自杀行为显著增加[25-26]。同时发现童年期创伤的个体发生代谢综合征患病率增加[27]。可见童年期创伤对心身健康的影响可能贯穿于整个生命周期。

三、早年创伤事件、端粒长度与抑郁症的关系

端粒长度的缩短可能与抑郁症的发生有关。荟萃分析发现，抑郁症与缩短的白细胞端粒存在显著关联[28]。一项随访20年的大型前瞻性研究发现，端粒较长与情绪稳定有关[29]。此外，较短的端粒可能是老年人抑郁症状严重程度的生物学标志[30]。端粒长度缩短加速可能是抑郁症发生的病因[31-32]。

荟萃分析也显示抑郁情绪、创伤经历与端粒长度缩短显著相关[5]。童年期虐待、抑郁症与表观遗传学衰老之间密切关联[33]，端粒长度类似于细胞的时钟，会影响细胞衰老的速度。与健康人相比，抑郁症患者在血液和脑组织中出现较高的表观遗传衰老现象，尤其在童年期遭受创伤后更为突出[34]。同样，Incollingo Rodriguez等[35]发现文化生活适应压力可能通过缩短端粒长度导致产后抑郁症。可见，端粒是重要的介质，慢性心理压力通过端粒长度变化可能导致包括抑郁症等精神疾病在内的疾病。然而，目前没有一个综合模型来描述压力生理学和神经内分泌途径的变化如何导致端粒生物学的变化[36]。以下机制可能在其中发挥了重要作用：

1.下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)：荟萃分析发现，高压导致的皮质醇反应与较短的端粒长度相关[37]。动物研究发现，暴露于糖皮质激素环境的鸟类显现更短的端粒或更

快的端粒损耗。因此，不良的生活事件可能导致HPA轴过度激活，引起糖皮质激素增加，代谢的增加减少了维持端粒长度所需的资源，在长期应激状态下增加了端粒大量磨损[38]。Gotlib等[39]报道过度的皮质醇反应与端粒长度缩短和抑郁症发生高度相关。

2.端粒酶活性改变：端粒酶活性改变也是影响端粒长度的重要元素。端粒酶是由一个RNA亚基和一个逆转录酶亚基组成的全酶，其主要细胞功能是将端粒重复序列添加到染色体末端延长端粒[40]。然而，当个体处于慢性或反复应激状态下端粒酶活性逐渐降低，导致端粒加速缩短[41]，这可能导致心身疾病和抑郁、焦虑情绪发生的重要因素之一[11]。

3.炎性因子：Pusceddu等[42]在人体研究中发现，促炎细胞因子水平升高与端粒长度较短有关，IL-6和超敏C反应蛋白(high-sensitivity C-reactive protein，hs-CRP)浓度较低的受试者端粒最长[43]。而不良生活事件可能诱导抑郁症的早年发病，部分可能是由于血浆IL-6水平升高介导的。不良生活事件导致的低度慢性炎症可能引发过早的生物老化，导致端粒的长度缩短[40]，诱导抑郁症的发生[35]。

4.氧化应激：氧化应激被认为是端粒缩短的主要原因。Michels等[44]发现儿童遭受虐待会激活氧化应激过程，线粒体是产生活性氧的主要场所，线粒体活性变化会显著增加活性氧水平，并引起氧化应激[45]，而端粒对氧化应激的损伤十分敏感，因此，线粒体损伤可直接导致端粒的缩短。线粒体功能障碍可引发持续的二次超氧化物和过氧化氢的产生，这会导致端粒的功能障碍[46]。氧化应激和抑郁症的发生密切相关，不良生活事件可能通过氧化应激的增加，加速端粒长度的缩短，从而增加抑郁症的患病风险。

四、总结与展望

综上所述，早年创伤事件、端粒长度和抑郁症之间的关系较为复杂。暴露于不良生活事件，尤其是生命早期的创伤事件，可能导致端粒磨损而增加抑郁症的发病风险。此外，也有部分文献支持抑郁症导致端粒长度缩短，这与本文的观点并不矛盾，易感性个体可能在抑郁发作前就已经存在端粒缩短现象，随疾病的发生与进展，精神创伤的负荷刺激，进一步加速端粒的缩短。因此，早期预防、识别和干预生命周期中的各类创伤事件，尤其是生命早期的创伤事件十分重要，需要进一步明确早年创伤事件与端粒长度变化的关联机制，提高细胞群平均端粒长度的测定精准度，可能对防止生命周期各种创伤或应激状态下抑郁症的发生具有重要的临床意义。

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 论文构思与设计为陈欢、王学义，文献收集及整理为刘不凡、黄凡凡，文章撰写为陈欢，文章审校与修订为王学义

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· 综述 ·

常见抗精神病药物对儿童青少年患者血清催乳素水平影响的研究进展

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【摘要】 高催乳素血症(HPRL)是儿童青少年精神障碍患者使用抗精神病药物的常见不良反应，会影响儿童青少年的正常发育，出现骨质发育障碍、月经失调等临床表现，从而降低患者的生活质量和用药依从性，影响患者的预后，加重社会的经济负担。因此，早期识别和及时干预HPRL具有重要意义。本文对常见抗精神病药物对于儿童青少年精神障碍患者血清催乳素水平的影响、HPRL可能的作用机制和治疗方法进行综述，旨在了解儿童青少年患者催乳素波动的特点和机制，为其个体化治疗提供一定依据。

【关键词】 高催乳素血症； 儿童； 青少年； 精神障碍； 抗精神病药物； 综述
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Research progress on the effect of common antipsychotics on serum prolactin levels in child and adolescents

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【**Abstract**】 Hyperprolactinemia is a common adverse reaction of antipsychotics in children and adolescents with mental disorders. It will affect the normal development of children and adolescents, such as skeletal dysplasia, irregular menstruation, etc, thereby reducing the quality of life and compliance, affecting the prognosis and increasing the socio-economic burden. Therefore, early identification and timely intervention are very important in clinical practice. This article reviews the effects of common antipsychotics on serum prolactin levels in children and adolescents, their possible mechanisms and treatment, aiming to investigate the characteristics and mechanisms of prolactin fluctuations in children and adolescents, and provide some basis for individual treatment.

【**Key words**】 Hyperprolactinemia; Child; Adolescent; Mental disorder; Antipsychotic; Review
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