Nursing Science 护理学, 2024, 13(5), 534-539
Published Online May 2024 in Hans. https://www.hanspub.org/journal/ns
https://doi.org/10.12677/ns.2024.135077

HPA轴与围产期抑郁症状的研究进展

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收稿日期：2024年4月15日；录用日期：2024年5月12日；发布日期：2024年5月21日

摘　要

孕妇在围产期经历了一系列的生理和心理变化，这些变化可能导致下丘脑－垂体－肾上腺轴的激活和功能紊乱；皮质醇因能反映下丘脑－垂体－肾上腺轴功能，成为探索围产期抑郁症与下丘脑－垂体－肾上腺轴关系的重要生物标记物，因此，可通过探索皮质醇在围产期抑郁症状病因和病理生理学中的具体作用为其早期识别和疗效预测提供依据。本文就下丘脑－垂体－肾上腺轴与围产期抑郁症状的研究进展进行综述，旨在为国内相关研究设计和实施提供帮助。

关键词

HPA轴，围产期抑郁症状，产前抑郁，产后抑郁

Research Progress of HPA Axis and Perinatal Depressive Symptoms

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Received: Apr. 15th, 2024; accepted: May 12th, 2024; published: May 21st, 2024

Abstract

Pregnant women undergo a series of physiological and psychological changes during the perinatal

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文章引用: 李星星, 周梦佳, 刘李, 肖归, 张婷婷, 张瑜, 秦春香, 陈正英. HPA 轴与围产期抑郁症状的研究进展[J]. 护理学, 2024, 13(5): 534-539. DOI: 10.12677/ns.2024.135077

period, which may lead to the activation and dysfunction of the hypothalamic-pituitary-adrenal axis. Since cortisol can reflect the function of the hypothalamic-pituitary-adrenal axis, it has become an important biomarker to explore the relationship between perinatal depression and the hypothalamic-pituitary-adrenal axis. Therefore, exploring the specific role of cortisol in the etiology and pathophysiology of perinatal depression symptoms can provide a basis for its early recognition and curative effect prediction. This article reviews the research progress of hypothalamic-pituitary-adrenal axis and perinatal depressive symptoms, in order to provide help for domestic research design and implementation.

Keywords

HPA Axis, Perinatal Depressive Symptoms, Prenatal Depression, Postpartum Depression

1. HPA 轴定义及生理

下丘脑－垂体－肾上腺(hypothalamic-pituitary-adrenal, HPA)轴是一种神经内分泌系统，它由一连串的神经内分泌途径组成，通常在快速反应和压力的情况下发挥稳定作用，而这种平衡主要是通过控制糖皮质激素的循环水平来实现的[1]，糖皮质激素在炎症、新陈代谢、认知、情绪、生殖、压力和心血管功能的调节中起着重要作用，其中皮质醇(CORT)是人类主要的下游糖皮质激素，具有包括调节情绪等多种生理功能[2]。体内的 CORT 水平由位于下丘脑室旁核(PVN)中的一组促肾上腺皮质激素释放激素(CRH)神经元控制，PVN 的促肾上腺皮质激素，促肾上腺皮质激素释放激素(CRH)和精氨酸加压素(AVP)激素刺激垂体前叶释放促肾上腺激素(ACTH)，ACTH 刺激肾上腺皮质释放 CORT [3]。HPA 轴活动受正前馈和负反馈回路的调节，正前馈回路包括 CRH 刺激垂体释放 ACTH 和刺激肾上腺分泌 CORT 的 ACTH。负反馈回路由 CORT 作用于大脑和垂体介导，分别抑制 CRH 和 ACTH 释放，以确保皮质醇相对快速地恢复到基线浓度[4]。

CORT 以脉动模式分泌，脉冲振幅的变化产生昼夜节律模式，在急性应激期间，皮质醇水平升高并维持搏动[5]。虽然皮质醇的最初升高是在 ACTH 水平大幅飙升之后出现的，但如果发生长期炎症应激，ACTH 水平会恢复到接近基础水平，而 CORT 水平会因肾上腺敏感性增加而保持升高[6]。在慢性应激中，垂体的下丘脑激活从 CRH 为主变为 AVP 为主，CORT 水平保持升高，至少部分原因是 CORT 代谢降低[7]。

基础活性代表激素的基线或静息状态水平，这通常以 24 小时的平均水平来衡量[8]。昼夜节律模式指的是在 24 小时周期内观察到的荷尔蒙分泌水平[9]。基础 HPA 轴激素在清晨达到峰值，CORT 最高峰值出现在醒来后 30~45 分钟，然后荷尔蒙在一天中下降到大约午夜时分的最低点[10]。用于测量昼夜节律模式的指标包括皮质醇觉醒反应(CAR) (皮质醇水平从醒来到醒来后约 45 分钟的变化)、昼夜斜率(DCS) (从清醒到睡眠的皮质醇水平的线性变化)和全天皮质醇分泌总量(曲线下面积(AUCg)) [11]。

2. 妊娠期 HPA 轴功能改变

妊娠期女性 HPA 轴会发生剧烈变化，垂体大小增加一倍，垂体肽的产生随着妊娠的进行而增加数倍

[12]。到妊娠第 7 周胎盘开始合成胎盘 CRH (pCRH)人胎盘合成，并在整个妊娠期间急剧增加[13]。在非妊娠情况下，糖皮质激素对下丘脑中 CRH 基因的表达具有抑制作用，相反的是，糖皮质激素能激活胎盘中的启动子区域，并对 CRH 的合成具有兴奋作用，从而导致整个妊娠期间母体 ACTH、CORT 和 pCRH 的急剧增加[14]。pCRH 刺激女性的脑垂体释放 ACTH，进一步提高女性的皮质醇水平，妊娠期间母体血清总皮质醇从平均 390 ± 22 nmol/L (第 5 周)增加到 589 ± 15 nmol/L (第 20 周) [15]。

妊娠中期开始，CRH、ACTH 和 CORT 开始上升，在妊娠晚期，母体皮质醇水平可达到非妊娠水平的约 2 至 5 倍，然后在婴儿分娩前达到峰值在分娩后急剧下降，可能在产后 3 个月恢复正常[16] [17]。在妊娠的最后几周，胎儿肾上腺产生大量的皮质醇，这可能标志着胎儿器官的成熟以及分娩的时间[18]。

3. 与围产期抑郁相关的 HPA 轴改变

围产期抑郁(Perinatal Depression, PND)指女性在妊娠期间和(或)产后出现的抑郁症状，是围产期常见的心理健康问题，根据美国精神病学会《精神疾病的诊断与统计 DSM-V》[19]，围产期抑郁的临床表现为情绪低落或在日常活动中失去兴趣超过两周，并伴有易疲劳、体重显著变化、失眠或嗜睡、精神运动性躁动或迟钝、无价值感或内疚感、注意力难以集中与自杀倾向等五种或五种以上症状，并根据首次发病时间将围产期抑郁分为产前抑郁(Antenatal Depression, AD)和产后抑郁(Postnatal Depression, PD) [20]，产前抑郁是指在怀孕期间出现的抑郁症状，在孕期持续 2 周以上的情绪低落和兴趣丧失、感到被孤立和隔离、社会活动功能丧失、不能控制自己的情感和行为的精神疾病综合征[21]，产后抑郁则是指女性在分娩后出现的抑郁症状，针对截尾时间有产后 1 周、4 周和 1 年的定义[22]，主要表现为产妇出现精神与行为失调及异常心理状态。

许多研究认为 HPA 轴在围产期抑郁的发病中起着重要作用[23] [24] [25]。孕妇在围产期经历了一系列的生理和心理变化，这些变化可能导致 HPA 轴的激活和功能紊乱；正常情况下，由于皮质醇水平高，应激反应功能良好的女性在妊娠期间对外部应激源的反应会降低，因为细小细胞室旁核中 CRH 神经元的激活减少[26]，在 HPA 轴失调的女性中，可能这种减弱不会发生，从而导致高皮质醇血症，反过来，高皮质醇血症会增加女性出现抑郁症状的风险[19]。

同时有研究认为妊娠期间皮质醇水平过高会导致产后抑郁，这是由于皮质醇血症引起的，考虑是分娩后 pCRH 的迅速消失以及下丘脑 CRH 的短暂抑制所导致的[27] [28]。但也有研究人员认为，身体通常会在产后自我适应这种戒断，在产后抑郁症的情况下，会发生过度调整，从而导致低皮质醇血症并引发抑郁症状[29]，并认为低皮质醇血症与母亲情绪之间的这种关系是由皮质醇和多巴胺能系统之间的相互作用介导的[30]。

4. 产前抑郁相关的 HPA 轴改变

皮质醇水平与产前抑郁有关。有研究[31]调查了 101 名处于孕中期和孕晚期的孕妇，结果表明抑郁与皮质醇水平升高有关；O’Keane 等人[32]报告说，患有抑郁症的孕妇的夜间皮质醇分泌持续较高，也导致全天皮质醇下降。

CAR、AUCg 和 DCS 都与产前抑郁有关。2018 年的一项系统评价[33]表明，与抑郁症状较少或没有抑郁症状的女性相比，患有抑郁症的孕妇皮质醇水平较高，CAR 减弱或减少；Epstein 等[34]人的研究调查了孕 26 周时的唾液皮质醇与抑郁症状，结果表示 CAR 减少和 AUCg 升高与抑郁症状有关；Shaimaa 等[35]的研究也认为患有抑郁症状的孕妇 CAR 减少，且提示其昼夜节律发生了紊乱；但有综述总结了 47 项研究后表示皮质醇觉醒反应与抑郁症状呈正相关，但在重度产妇抑郁症的情况下会减弱[36]。针对孕期 DCS 与抑郁症状的关系，研究[31]发现，与非抑郁孕妇相比，抑郁孕妇的皮质醇斜率更平坦/受抑制。总

之，怀孕期间抑郁症的特征似乎反映了皮质醇分泌水平和总量较高、皮质醇觉醒反应迟钝/减弱以及皮质醇斜率减弱/平坦。

调查了 365 名孕妇孕晚期和产后第 6 周的夜间皮质醇水平、抑郁症状，与对照组相比，患有产后抑郁的女性夜间皮质醇更高，皮质醇水平与产后抑郁症状呈正相关，且与产前和对照组有抑郁症状的女性对比，有产后抑郁症状的女性产后皮质醇水平更高[37]。

5. 产后抑郁症相关的 HPA 轴改变

在产后的前 2 个月，大多数研究报告了与抑郁症相关的皮质醇水平较高，包括全天[38]以及早晨[39]和晚上[40]。调查了 365 名孕妇孕晚期和产后第 6 周的夜间皮质醇水平、抑郁症状，与对照组相比，患有产后抑郁的女性夜间皮质醇更高，皮质醇水平与产后抑郁症状呈正相关，且与产前和对照组有抑郁症状的女性对比，有产后抑郁症状的女性产后皮质醇水平更高[37]，Conde 等[41]学者的研究也是如此结论。据报道，在产后 6 个月[24] [42]也报告了较高的夜间皮质醇。

Elizabeth 等[38]的研究分别在妊娠第 3 个月和分娩后第 7 天和第 14 天以及第 1、2、3 和 6 个月采集了唾液皮质醇，最终发现产后 14 天的 AUCg 是产后抑郁症状的预测因子，AUCg 增加一个单位，产后抑郁得分增加 2.16；一项调查产后 6 个月女性唾液皮质醇的研究[24]表示患有产后抑郁的女性 CAR 显著低于正常产后妇女、非产后健康女性，且其 DCS 也较为平坦。最后，Scheyer 和 Urizar [43]报告了产后 3 个月的孕早期和孕中期 CAR 较低、孕中期的 DCS 更平坦。因此，与怀孕期间的抑郁症类似，迄今为止的大多数研究表明，产后抑郁症女性的皮质醇水平更高，CAR 变钝/减弱，昼夜斜率更平坦。

HPA 轴的改变可能部分是由于 PPD 患者难以应对应激源和维持体内平衡[44]。这可能是由垂体前叶、下丘脑和海马体中的皮质醇受体以及垂体前叶中的 ACTH 受体和下丘脑中的 CRH 自身受体介导的负反馈受损引起的[45]。一项系统评价报告说，检查 HPA 对应激源反应的研究表明，PPD 女性的 HPA 轴反应减弱[46]，表明 HPA 轴在调节急性应激方面存在低反应性。

综上所述，HPA 轴与围产期抑郁相关性仍需要进一步明确，总结以往研究，出现异质性的原因可能是各类研究中纳入的 PND 女性时期各不相同，或者是对抑郁症症状评估方法多样；以及各类研究控制的混杂因素也各不相同；探索皮质醇与 PND 的关系有助于对 PND 发生的机制进一步明确，因此，未来的研究可考虑对两者关系的探索放宽至 PND 全程。

基金来源

吉首大学校级项目科研项目(Jdy22091)。

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