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Effects of Chronic Stress on Emotion and Neural Mechanism: Focus on Sex Difference

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Abstract

Chronic stress damages the body's health and is closely related to various mental and physical diseases such as anxiety, depression, schizophrenia, cardiovascular disease and cancer. The brain regions involved in the stress response are mainly the prefrontal cortex, hippocampus and amygdala, which not only modulate the stress response but also influenced by stress. The effects of chronic stress on the body show gender differences. This article will review sex differences in the effects of chronic stress on emotional function in human and animal models, including the structure and function of related brain regions and sex hormones, the effects on neuronal function, and specific mechanism.

Keywords

Chronic Stress, Depression, Anxiety, Sex Difference, Neural Circuit

性别在慢性应激影响情绪功能中的作用及其机制

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摘　要

慢性应激损害机体健康，与焦虑症、抑郁症、精神分裂症、心血管疾病和肿瘤等多种精神和躯体疾病密

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切联系。参与应激反应的脑区主要有，前额叶皮质、海马和杏仁核。这些脑组织不仅调制应激反应，也受应激的影响。慢性应激对机体的影响表现出性别差异。本文将综述在人类和动物模型上慢性应激对情绪功能影响的性别差异，包括相关脑区结构和功能及性激素，对神经元功能的影响，探讨性别差异机制。

关键词

慢性应激，抑郁，焦虑，性别差异，神经环路

1. 前言

研究表明，60%以上病人的就诊原因与应激相关。急性应激会在一定程度上促进个体的认知功能，慢性应激会改变大脑结构，损害功能，引起精神及躯体疾病(Cohen, Janicki-Deverts, & Miller, 2007; McEwen, 2008; Russo, Murrough, Han, Charney, & Nestler, 2012)。前额叶、海马、杏仁核三个脑区与慢性应激影响情绪功能有密切联系。前额叶(PFC)是具有高级“执行”功能的大脑区域，如工作记忆，注意力，决策和情绪控制(Davidson, Putnam, & Larson, 2000; Goldman-Rakic, 1995; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004)。杏仁核是情绪情感形成的关键脑区(Ebner, Rupniak, Saria, & Singewald, 2004)，与额叶皮质形成的通路与恐惧情绪有关(Davis & Whalen, 2001)。海马是调节应激反应的重要部位(Fanselow & Dong, 2010; Padilla-Coreano et al., 2016)，激素水平过高会导致海马功能障碍，引发情绪相关精神疾病，如双相情感障碍和抑郁症(Bonne et al., 2008; Frey et al., 2007; Herman et al., 2003; McEwen et al., 1997)。当个体处于长期应激会引起下丘脑－垂体－肾上腺(HPA)轴分泌糖皮质激素失调，损害前额叶皮质(PFC)对边缘区域的控制能力(Adhikari et al., 2015; Kumar et al., 2013; Sotres-Bayon, Bush, & LeDoux, 2004)，减弱海马对 HPA 轴的调节作用(Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009)，过分增强杏仁核功能(Arnsten, 2009)，导致糖皮质激素受体介导的负反馈受损，HPA 轴的持续亢进(Gregus, Wintink, Davis, & Kalynchuk, 2005)。临床研究发现，焦虑和抑郁症病人皮质醇分泌过高(Bangasser & Valentino, 2014; Deuschle et al., 1997; Holsboer, 2001; Nestler et al., 2002; Young & Korszun, 1998)，前额叶皮质和海马区域体积减少、激活水平下降，杏仁核活动过度增强(Russo et al., 2012; Drevets, 2003; Oakes et al., 2004)；重度抑郁(MDD)患者病理切片发现，PFC、杏仁核区域神经元和胶质细胞密度下降，神经元的体型缩小(Bowley, 2002; Drevets, 2000; Hamidi, Drevets, & Price, 2004; Ongur et al., 1998; Rajkowska et al., 1999)；背外侧前额叶(dlPFC)的 GABA 水平的降低，尤其是 SST mRNA 表达下调，以及海马的脑源性生长因子(BDNF)与其前体蛋白 TrkB 水平降低(Guilloux et al., 2012; Maciag et al., 2010; Rajkowska, O'Dwyer, Teleki, Stockmeier, & Miguel-Hidalgo, 2007; Sibille, Morris, Kota, & Lewis, 2011; Tripp, Kota, Lewis, & Sibille, 2011; Tripp et al., 2012)，MMD 患者的 dlPFC 脑区的谷氨酸能基因表达水平增加(Gray, Hyde, Deep-Soboslay, Kleinman, & Sodhi, 2015)。动物模型进一步发现，暴露于慢性束缚应激(CRS)的大鼠海马 CA3 区锥体神经元的顶端长度和分支点明显减少(Dias-Ferreira et al., 2009)，长时间的心理应激和伴随血液皮质醇升高会诱导海马和前额叶皮质(PFC)中的代谢减少和突触密度降低(Gregus et al., 2005)，海马体积缩小和齿状回神经元形成减少(Czeh et al., 2001; Gould & Tanapat, 1997)，杏仁核的树突肥大(Adhikari et al., 2015)，此外发现长时间的严重应激导致谷氨酸释放从前额叶皮质(PFC)中的锥体神经元向基底外侧杏仁核(BLA)中的GABA能中间神

经元的减少，BLA 主神经元的过度兴奋(Wei, Zhong, Qin, Tan, & Yan, 2017)，同时慢性不可预测应激(UCMS)降低大鼠 PFC 中突触蛋白 I，钙调蛋白 2，Rab3A 和 Rab4B 的表达，增加 PFC 中的转录抑制因子 GATA1 表达，上调小鼠杏仁核中的神经刺激肽前体蛋白(HCNP-pp)的 mRNA 表达和乙酰胆碱酯酶(AChE)水平(Bassi, Seney, Argibay, & Sibille, 2015)。此外持续 21 天的慢性束缚会导致小鼠海马 kalirin-7 蛋白表达水平明显下降(Li, Li, & An, 2010)。

慢性应激在精神疾病的发病机制中产生的影响表现出明显的性别差异。流行病学研究表明，在社交焦虑症，广泛性焦虑症，恐慌症和创伤后应激障碍等精神疾病中，女性的发病率较男性更高(Maeng & Milad, 2015)。在 138 例(男性 111 例，女性 27 例)有创伤暴露史的可卡因依赖成年人中，男性的耐受性比女性高，而较差的耐受性与 PTSD 症状严重程度相关(Vujanovic, Rathnayaka, Amador, & Schmitz, 2016)，即女性 PTSD 患者病情更为严重。此外，重性抑郁症(MDD) (Wang, Lin, Song, Sibille, & Tseng, 2012)的影响在不同性别间存在显着差异，女性抑郁症的终生患病率比男性更高(Cyranowski, Frank, Young, & Shear, 2000; Kessler, 2003; Sloan & Sandt, 2006)。患 MDD 的女性症状也比男性更严重(Plaisier, Taschereau, Wong, & Graeber, 2010; Zeisel et al., 2015)，特别是睡眠过多和体重增加(Chang et al., 2014; Guilloux et al., 2012; Sibille et al., 2004; Sibille et al., 2009)，MDD 并发症也有差异，如焦虑症状(Seney et al., 2018)。以上这些研究结果表明女性对情绪精神疾病的更加易感，症状更多且严重、持续时间更长。

本综述主要阐述性别差异在慢性应激中的情绪行为的影响，探究性腺激素、脑区结构与功能在应激反应所起作用。

2. 应激反应的性别差异

应激反应中男女大脑结构功能的不同，与临床发现结果具有高度的相关性(Milad, Igoe, Lebron-Milad, & Novales, 2009)。影像学研究发现，女性应激后在右腹侧前额叶的合氧血红蛋白含量(oxy-Hb)相比男性明显增加，额极脱氧血红蛋白反应(deoxy-Hb)与焦虑水平显着相关(Marumo, Takizawa, Kawakubo, Onitsuka, & Kasai, 2009)。抑郁症男性患者在前额叶－纹状体回路中存在异常，尾状核灰质密度显着减少；女性的杏仁核和海马灰质密度减少(Hastings, Parsey, Oquendo, Arango, & Mann, 2004; Kong et al., 2013)。病理研究发现，抑郁症女性患者杏仁核的 BDNF mRNA 及其蛋白水平显着下调，胆碱能神经刺激肽前体蛋白(HCNP-pp)mRNA 水平上调(Bassi et al., 2015; Guilloux et al., 2012; Puralewski, Vasilakis, & Seney, 2016)。女性 MDD 患者的 dlPFC 中检测到谷氨酸能基因(GRIN1，GRIN2A-D，GRIA2-4，GRIK1-2，GRM1，GRM4，GRM5 和 GRM7)有更高表达水平，而男性 MDD 患者的 GRM5 表达较低(Gray et al., 2015)。基因荟萃研究发现，MDD 患者背外侧前额叶皮层，亚前扣带皮层(sgACC) (Tripp et al., 2012)，以及杏仁核和基底核中 SST (生长抑制激素)基因表达减少且存在性别差异(Guilloux et al., 2012)，即女性患者 sgACC 中的 SST 减少更为明显(Seney et al., 2013)，同时 SST 表达仅在女性的杏仁核中呈减少趋势(Guilloux et al., 2012; Sibille et al., 2009)。Seney 等人发现 52 个基因在 MDD 男性和女性之间显示相反方向的表达变化，其中 MDD 总体转录谱在男性和女性中表现相反；MDD 男性杏仁核突触相关基因减少，而 MDD 女性却表现出转录增加；患有 MDD 的男性 dlPFC 和 ACC 表现出少突胶质细胞和小胶质细胞相关基因的增加，而具有 MDD 的女性在这些细胞类型的标记物中有所减少(Seney et al., 2018)。虽然抑郁症患者的整体海马体积没有性别差异(Yucel et al., 2009)，但对抗抑郁药物反应不敏感的女性海马体积比对治疗有反应的女性要小，这种效应在男性中没有观察到(Vakili et al., 2000)。

虽然在精神疾病男女性患者中观察到的脑组织结构功能和基因表达变化确实表明不同性别间潜在环路的差异，但是由于绝大多数成像研究采用横断面设计、相关研究以及技术限制，因此很难确定结构性别差异与疾病流行之间的因果关系。所以科学家已转向临床前模型，以开始解决这些关系的性质，以及

调查无法用人类当前方法评估的细胞分子层面的性别差异。

3. 慢性应激动物模型的行为的性别差异

慢性轻度应激(CMS)后雌性大鼠蔗糖消耗量明显降低，木僵时间显着增加(LaPlant et al., 2009)，旷场实验中活动性降低(Autry, Adachi, Cheng, & Monteggia, 2009; Dalla et al., 2005; Monteggia et al., 2007; Xing et al., 2013)。R. Shepard 等人发现，2 周的慢性不可预知应激(UCMS)后雌性大鼠在强迫游泳中表现出更高的木僵率和更短的木僵不动出现的潜伏时间，在旷场实验中应激后雌性停留在中心时间更少且活动性降低(Shepard, Page, & Coutellier, 2016)。在慢性社会挫败心理应激的动物模型中，被击败雌鼠在强迫游泳测试中的潜伏期缩短，木僵时间增加，社交时间减少及皮质酮释放增加，这表明雌性在社交挫败后更容易出现抑郁行为，在焦虑水平上无明显性别差异(Weathington, Arnold, & Cooke, 2012)。Watt 与其同事发现，青春期暴露于社交挫败后，成年雄性大鼠在高架十字迷宫和旷场中的自发活动增加(Watt, Burke, Renner, & Forster, 2009)。而在慢性足底电击应激后，只有雄性大鼠表现出习得无助行为(Dalla, Pitychoutis, Kokras, & Papadopoulou-Daifoti, 2011; Shors et al., 2007)。Karisetty 等人发现慢性可变轻度应激(CVMS)会导致雌性小鼠产生快感缺失(蔗糖消耗减少)，但雄鼠和 OVX 雌鼠未发现这种行为的变化(Karisetty, Joshi, Kumar, & Chakravarty, 2017)。持续三周慢性不可测应激导致青年期雌性大鼠表现出糖水消耗量减少，高架十字测试中活动过度，强迫游泳测试中木僵潜伏期缩短且挣扎次数减少，且行为变化持续到成年期，而青年期应激后雄鼠未表现出明显的行为改变(Bourke & Neigh, 2011)。持续 6 天的亚慢性可变应激(SCVS)致使雌性小鼠梳理毛发行为显著减少，在新异性抑制喂养测试中进食潜伏期增加，糖水消耗减少，而应激后雄性小鼠并无行为变化(Hodes et al., 2015)。

以上众多的慢性应激动物模型的行为学两性差异(Kokras & Dalla, 2014)，证实应激相关精神疾病的性别双向性，表明其行为背后潜在机制可能来自慢性应激后脑区结构功能、神经环路、性激素、突触传递间不同的变化。

3.1. 慢性应激后不同脑区变化的两性差异

相较于关注皮质边缘脑区体积变化的人类研究，动物模型通常侧重于识别脑区神经元功能与传递的变化。慢性束缚应激引起雌性大鼠的腹侧海马 CA1 锥体神经元树突棘密度减少，在雄性动物中没有发现这种变化；但应激造成雄性海马 CA3 区神经元顶端树突的萎缩。持续 21 天的束缚应激后会使雄性大鼠的内侧 PFC 中的神经元显示出树枝状的分枝和收缩，雌性皮质区域的树突没变化(Luine, 2002; McEwen & Milner, 2007; Wellman, 2001)。但从内侧 PFC 投射到杏仁核的神经元会在雌性体内经历树突扩张，这种扩张可能依赖于雌激素，因为卵巢切除的雌性(OVX)并没有表现出这种变化(McEwen & Morrison, 2013)。Garrett 等人也发现在对 SD 大鼠进行每天三小时持续一周的束缚应激后，雄性的内侧前额叶顶树突分支和长度减少，雌性却表现为顶端树突的长度的增加，而雌性的树突变化依赖于雌二醇 E2 (雌激素的一种，由卵巢分泌) (Garrett & Wellman, 2009)。慢性应激减少雄性的额叶皮层和杏仁核的多巴胺能活性，增加雄性海马 CA3 区中的 γ 氨基丁酸(GABA)水平；增加雌性 CA3 区中的五羟色胺(5-HT)和去甲肾上腺素(NE)的水平(Luine, 2002; McEwen & Milner, 2007; Rico et al., 2015; Wellman, 2001)。慢性轻度应激降低雌性大鼠前额叶皮质区域的多巴胺能活动以及海马区域的五羟色胺能活动(Dalla et al., 2005; LaPlant et al., 2009)。在慢性不可控足底电击后，发现只有雄性大鼠海马区域表现出新生神经元形成减少和五羟色胺能活动增加(Amat et al., 2005; Bland, Schmid, Greenwood, Watkins, & SF, 2006; RP, 1991; Shors et al., 2007)。Reich 等人发现慢性不可预测应激导致雄性小鼠海马区域的大麻素受体 1 (CB1)下调，尤其是在背侧海马比腹侧海马更加明显，与之不同的是雌性小鼠在应激后腹侧海马 CB1 显着上调，表明雄雌动物的内源性大麻素(eCB)

系统在慢性应激后的反应存在偏向性(Reich, Taylor, & McCarthy, 2009)。持续一周重复应激使雄鼠 PFC 锥体神经元的谷氨酸能传递和谷氨酸受体膜表面表达减少，但雌性却未见改变，通过阻断雌鼠的芳香酶(合成雌激素所需的生物酶)或给予雄鼠注射雌二醇，发现雌激素可以防止应激对谷氨酸传递产生有害影响(Wei et al., 2014)。有研究还发现慢性应激也会导致动物在基因表观遗传方面存在两性差异，Nollet 等人发现在不可预测慢性应激(UCMS) (Nollet, Le Guisquet, & Belzung, 2013; Willner, Muscat, & Papp, 1992)后，伴有严重情绪缺陷的雌性动物的前额叶活动减退，内侧杏仁核(BMA)的即刻早期基因(c-Fos)细胞会减少，外侧杏仁核的 c-Fos 表达却增加；前额叶皮层中的 γ-氨基丁酸能(GABAergic)传递的 mRNA 表达增加与雌性的焦虑和抑郁行为有密切相关，即在谷氨酸脱羧酶 67 (GAD67)的 mRNA 表达和第 1 次不动的潜伏期之间观察到显着的正相关；在小清蛋白(PV)的 mRNA 表达和在中心区域的时间之间观察到显着的负相关。而在 UCMS 后雄性中，只发现在前额皮层中 GAD67 mRNA 表达有短暂的增加，所以雌性前额叶 PV 系统对应激的脆弱性增加可能成为应激相关情绪障碍患病率和症状的性别差异的基础(Shepard et al., 2016)。慢性不可测应激会使雌性大脑中心区域的 crf 基因甲基化位点特异性改变，而这种变化则发生在雄性的杏仁核(CeA)及床核(BST)区域；雌性 BST 区的组蛋白乙酰转移酶和 CREB 结合蛋白水平上升，而雄性 CeA 区去乙酰化酶 5 水平下降(Sterrenburg et al., 2011)。慢性可变轻度应激只引起雌性小鼠 PFC 脑区的 BDNF 蛋白水平下调，CRH，NR3C1，CART 以及 NPY 等应激相关基因表达水平的上升，但这种基因水平的变化未出现在雄鼠和 OVX 雌鼠身上(Karisetty et al., 2017)。

从以上应激后脑区能两性差异，表明性腺激素在其中所起的重要作用以及慢性应激在不同性别个体之间参与调节的神经环路存在一定的差别。

3.2. 参与慢性应激调节的神经环路的性别差异

慢性应激诱导的前额叶功能异常，会损害其对边缘区域的控制作用，可能与情绪障碍的发生有关。Shepard 等人发现在 UCMS 后的雌性在 BMA 中 c-Fos 的激活水平降低和 BLA 的功能亢进，都可能源于雌性小鼠 PFC 对杏仁核(CeA)控制减退，而在应激后的雄性小鼠中却发现抑郁行为的产生可能与 PFC-伏隔核(NAc)环路的谷氨酸能递质传递受损相关，因为相比于对照组，在旷场实验后应激雄鼠 NAcc 中的 c-Fos 阳性细胞明显减少，但由于 NAcc 还接收其他脑区的神经元投射，特别是腹侧海马(vHIP)-NAc 环路参与调控慢性社会挫败导致抑郁行为的易感性(Bagot et al., 2015; Shepard et al., 2016)，所以参与雄性小鼠产生情绪状态的调节的神经环路可能是多重的。目前对于海马相关神经环路(HIP-PFC/BLA)与应激后情绪障碍的两性差异研究十分缺乏，大多研究发现关注于雄性应激后海马 CA1/3，DG 区神经元形态变化(Anacker et al., 2018; Naninck et al., 2015)，情绪产生机制或糖皮质激素与海马之间的联系(Padilla-Coreano et al., 2016; Sairanen, O'Leary, Knuuttila, & Castren, 2007)，应激后认知功能与海马细胞分子变化间的关联(Galea et al., 1997; Zer-Aviv & Akirav, 2016)。

总的来说，在不同性别个体慢性应激后，神经环路的变化是不同的，即存在性别双向性。并且值得研究者更加深入地挖掘和区分其中的变化，为从神经环路层面去干预性别偏向性的精神疾病提供更多的实证依据。

4. 性腺激素差异在慢性应激后情绪行为的影响

在性腺激素中，雌激素在情绪产生中的作用得到广泛研究(Epperson, Kim, & Bale, 2014; Jacobs et al., 2015; Shanmugan & Epperson, 2014)。例如 Schiller 等人发现雌二醇调节围产期的女性和雌性动物的抑郁行为(Schiller, O'Hara, Rubinow, & Johnson, 2013)。而且长期卵巢切除(OVX)会增加 CUS 后小鼠的抑郁和焦虑行为，损害海马的细胞增殖(Lagunas, Calmarza-Font, Diz-Chaves, & Garcia-Segura, 2010)。此外 Li 等

人发现持续注射雌激素可以逆转雌性小鼠在慢性束缚应激后产生的抑郁行为(Li et al., 2010)。尽管大多数研究表明雌激素发挥抗抑郁作用，但性腺激素水平的循环似乎不是绝对水平，而是更显著地与女性生殖阶段特异性抑郁综合征有关，这可能导致女性更易患抑郁症(Yoon & Kim, 2018)。雌激素易随外界环境和个体年龄的不同产生周期性改变。妇女对情绪障碍的易感性增加常发生在青春期后，随着卵巢 E2 (雌激素雌二醇)分泌的周期性变化开始(Hayward & Sanborn, 2002; Kessler & Walters, 1998; Lewinsohn, Gotlib, Lewinsohn, Seeley, & Allen, 1998; Walf & Frye, 2006)，抑郁症妇女血浆 E2 水平显着地降低(Young, Midgley, Carlson, & Brown, 2000)。因此，E2 波动可以影响女性情绪障碍的发病率或症状学的产生。如手术或自然绝经发生的 E2 水平的显著变化与焦虑和抑郁症的发病率和症状的变化相关。随着年龄的增长，产生内源性 E2 水平的降低可能与焦虑和抑郁症有关(Walf & Frye, 2006)。E2 水平在啮齿动物的焦虑和抑郁的性别差异起到部分作用(Palanza, 2001)。但雌性不处在发情周期时，与雄鼠的焦虑和抑郁水平无差异(Walf & Frye, 2006)。在慢性不可预测应激后，OVX 大鼠下丘脑 ERα-mRNA 水平升高，可能引起 E2 与 ER(-α)的结合增加，刺激中枢应激神经肽 CRH 的转录，HPA 轴激活，从而导致情绪障碍(Bao, Hestiantoro, Van Someren, Swaab, & Zhou, 2005; Guo et al., 2018)。在慢性足底电击后雌性 OVX 大鼠腹侧前额叶神经元的细胞外信号调节激酶 1，2 磷酸化(pERK)表达增加，注射 E2 治疗可阻止这种应激诱导的 pERK1/2 升高，这可能会增强 mPFC 神经元活力和功能(Gerrits, Westenbroek, Koch, Grootkarzijn, & ter Horst, 2006; Kuipers, Trentani, Den Boer, & Ter Horst, 2003; Trentani, Kuipers, Ter Horst, & Den Boer, 2002)。Karisetty 等人发现注射 E2 可部分缓解 OVX 雌鼠由慢性应激引起的过度木僵行为，减轻快感缺失程度，提高 PFC 脑区的 BDNF 蛋白水平，促进 PFC 神经元的生长(Karisetty et al., 2017)。然而，雌激素可能是增加与情绪障碍相关的神经环路应激后敏感性的重要因素。众多研究发现雌性在长时间应激后，腹侧 PFC 区神经元形态不受影响，但投射到杏仁核脑区的神经元树突明显增加，而在 OVX 雌性中未发现如此变化，同时后期对其进行雌激素注射补充后，发现杏仁核区域神经元树突分枝也显着增加(Shansky et al., 2004; Shansky, 2006; Shansky et al., 2010; Yuen, Wei, & Yan, 2016)。因此雌性个体可能会对慢性应激源更加易感，更易产生焦虑抑郁样行为。

雄激素(包括睾酮，DHT，DHEA)的水平相对稳定并且在两性的中年期间逐渐减少，睾酮缺乏是老年男性抑郁症产生的原因之一。抑郁症患者睾酮水平低，尤其是在重度和难治性抑郁症患者以及老年人群中更为明显(Zarrouf, Artz, Griffith, Sirbu, & Kommor, 2009)。动物研究发现，海马中睾酮依赖于细胞外信号调节激酶 2 (ERK2)的表达，在切除性腺的雄性大鼠中海马 ERK2 活性减弱会诱导快感缺失，而 ERK2 的多表达阻止快感缺失，说明 ERK2 信号传导参与睾酮的抗抑郁药样作用(Carrier & Kabbaj, 2012; Yoon & Kim, 2018)。Wainwright 等人也发现睾丸素的信号传导缺失会加剧雄性大鼠在慢性轻微应激后的抑郁样行为，体重减轻和在海马的细胞增殖和存活以及神经可塑性蛋白 PSA-NCAM 的表达降低减少(Wainwright, Lieblich, & Galea, 2011)。在啮齿动物中，雌性显示出明显的生理应激反应，如皮质酮水平升高，雄性则无显着反应，这主要是由于青春期后活性睾酮对雄性 HPA 轴的全面抑制(Bale & Epperson, 2015; Bao et al., 2006)。Puralewski 等人也发现雄性小鼠通过睾丸激素的循环可以缓解由慢性轻微应激导致的杏仁核区域生长抑制激素(SST)表达下降，从而减轻焦虑行为(Puralewski et al., 2016)。在 PTSD 的研究发现脱氢表雄酮(DHEA)或 DHEA 与皮质醇比值表明雄激素在恢复性(抗压力)中的作用。在 PTSD 患者中，DHEA 对促肾上腺皮质激素(ACTH)的反应升高，与症状的严重程度呈负相关，表明应激时 DHEA 的释放可缓冲 PTSD 的严重程度(Rasmusson, Vythilingam, & Morgan, 2003)。另一项研究也发现，PTSD 中 DHEA 水平升高，但较高水平与症状改善和更好的应对相关，而较低的 DHEA 与皮质醇比例与 PTSD 症状的严重程度呈正相关(Yehuda, Brand, Golier, & Yang, 2006)。但是也有研究发现 DHEA 升高与男性退伍军人 PTSD 自杀率

上升相关(Butterfield et al., 2005; Russo et al., 2012)。因此，未来的工作需要确定 DHEA 是否确实是积极应对的一个因果因素。

总而言之，性腺激素差异在慢性应激后情绪行为的影响在一定程度上是双向的，在个体发展的不同阶段，性腺激素的周期性波动影响着个体应激反应和情绪疾病的易感性。

5. 总结

虽然男性和女性的精神疾病总体发生率几乎相同，但在不同的精神病理学中存在显着的性别差异。因此，研究应激的性别特异性机制，以及在抗压性/易受压力中的作用(Charney, 2004; Karatsoreos & McEwen, 2011; Russo et al., 2012)，在临床和临床前科学研究中得到关注。

大多数人类工作仅限于相关研究。根据上述动物研究，未来的人类研究应该关注机制研究。研究认知和情绪领域中与应激相关的缺陷脆弱性的性别差异。事实上，来自整个生殖期妇女的证据表明，波动的卵巢激素可能是这些疾病患病率增加的生物学机制。研究应激反应中性别差异的机制可以为我们提供关于抑郁症和焦虑症应对机制的独特生物学信息。

此外，人类和动物的数据表明，性别影响个体对应激身心反应(Bangasser & Wicks, 2017; Kokras & Dalla, 2014; Kudielka & Kirschbaum, 2005; Palanza, 2001; Palanza & Parmigiani, 2017)，这可能与个体自身性腺激素水平变化以及脑区的两性差异有关，普遍认为性别差异影响药物敏感性、活性和效果。对于性别差异影响精神疾病的机制研究及探讨，有助于靶向性药物的研发与治疗。

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