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焦虑和抑郁障碍的性别差异神经机制

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摘要 焦虑障碍和抑郁障碍具有显著的性别差异, 女性患病率明显高于男性. 本文综述了关于其性别差异性神经机制的研究进展. 基于人群的脑功能成像和组织学研究表明, 杏仁核、前额叶皮层和岛叶皮层等与情绪加工和调节相关的脑区在两性中存在显著差异. 临床用药研究发现针对5-羟色胺系统的抗抑郁药可能与两性疗效差异相关. 在动物模型研究方面, 雌性焦虑和抑郁疾病模型的建立, 包括母婴分离、改良的慢性社交挫败应激等, 为探究性别差异的神经机制提供了有力工具. 遗传和表观遗传分析进一步揭示了两性在基因表达调控和信号通路等方面的差异. 此外, 性激素和神经肽对两性神经环路的不同调控方式在焦虑和抑郁障碍的性别差异中也扮演着重要角色. 未来结合分子、细胞、环路和行为等不同层面的研究, 将有助于深入阐明焦虑和抑郁障碍性别差异的发病机制, 并据此开发性别特异性的诊断和治疗策略.

关键词 性别差异, 焦虑症, 抑郁症, 情感障碍

焦虑障碍(anxiety disorders)和抑郁障碍(depressive disorders)是当前广泛影响人类健康, 并带来极重医疗负担的精神疾病. 焦虑障碍的临床表现为持续性的焦虑和对未来无明确客观对象的担忧[1]. 抑郁障碍是一种更为严重的精神疾病, 其核心症状为情绪低落, 对日常活动缺乏兴趣, 伴随的症状包括产生无价值感、负罪感甚至自杀念头, 以及疲倦、睡眠紊乱、食欲不振、注意力不集中、精神活动迟缓和易激动等[2]. 近年来, 焦虑和抑郁障碍的发病率呈现逐年上升的状态. 特别是在年轻人群当中, 焦虑和抑郁障碍对人们的工作、生活带来严重的影响, 其中抑郁障碍甚至成为导致自杀的主要因素之一[3~5]. 当前焦虑障碍的发病率约为3.1%, 终身发病率可达5.7%[1]; 抑郁障碍发病率为6%左右, 终身发病率高达15%~18%[2]. 焦虑和抑郁障碍具有显著的两性差异, 且女性的发病率都两倍高于男性[6,7]. 女性抑郁障碍患者的病症严重程度和表现也与男性不同: 女性更易并发暴食、焦虑和嗜睡等症状; 男性则更易伴随酒精或药物成瘾[8,9]. 在焦虑障碍当中, 女性患者更常抱怨疲劳、肌肉紧张、心肺和胃肠不适等躯体症状[10]. 虽然焦虑和抑郁障碍的女性患者更为严重, 但是早年关于焦虑和抑郁障碍的神经机制研究多数只在雄性动物模型中开展. 这使得人们对于女性的发病机制缺少认识, 也缺乏对女性患者的治疗评估. 为了更好地治疗焦虑和抑郁障碍, 我们需要拓展两性通用的疾病模型, 在此基础之上探索两性共同和差异的发病机制与治疗方法.

1 基于焦虑和抑郁障碍人群的脑成像研究

基于人群的研究为揭示焦虑和抑郁障碍的两性差异机制提供了直接的相关性证据. 当前常用的研究方

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法包括脑功能成像、病理组织学组学分析和临床药理学评估等. 在已有的研究当中, 人们通过脑功能成像发现了多个与焦虑和抑郁障碍相关的脑区的激活程度和功能连接具有两性差异, 包括杏仁核(amygdala)、前额叶皮层(prefrontal cortex)、海马(hippocampus)和岛叶皮层(insular cortex)等[11].

杏仁核是情绪产生, 加工和调节的关键脑区, 在焦虑和抑郁障碍的发生发展中扮演重要角色. 多项研究表明杏仁核在情绪加工处理中存在显著的性别差异, 其中女性的杏仁核对负性情绪刺激更加敏感. 功能磁共振成像(functional magnetic resonance imaging, fMRI)研究发现, 在观看负性情绪图片时, 女性的杏仁核激活程度显著高于男性, 而在观看中性图片时, 两性的杏仁核激活程度没有显著差异[12]. 另一项fMRI研究发现, 在接受恐惧条件化任务时, 女性的杏仁核激活程度高于男性[13]. 神经影像研究还发现, 在加工负性情绪面孔时, 女性的左侧杏仁核激活程度显著高于男性; 而正向情绪对男性的左侧杏仁核激活显著高于女性[14]. 在焦虑障碍患者中, 女性表现出更高的杏仁核反应性和更强的恐惧记忆. 女性惊恐障碍患者在观看恐惧面孔时, 其杏仁核激活程度明显高于男性患者[15]. 除了情绪相关脑激活的性别差异外, 男女两性在负性情绪加工过程中, 相关脑区之间的功能连接也存在关键性别差异. 一项研究发现, 男性从右侧杏仁核到背内侧前额叶皮层的功能连接显著强于女性[16]. 这提示情绪在两性大脑网络中可能存在性别特异性的处理方式. 总的来说, 女性的杏仁核, 尤其是左侧杏仁核, 对负性情绪刺激更加敏感, 现出更高的反应性. 而男性则表现出更强的杏仁核-前额叶连接, 这可能反映了对情绪处理的更多评估性反应. 杏仁核在情绪加工和调节方面存在的显著性别差异, 可能与女性更易患焦虑和抑郁障碍有关.

前额叶和岛叶皮层在情绪信息处理中发挥关键作用. 前额叶皮层指的是位于初级和次级运动皮层前侧的额叶区域, 包含前扣带回皮层(anterior cingulate cortex)和眶额叶皮层(oribital frontal cortex)等分区. 前额叶皮层负责情绪调节、决策、执行功能和注意力控制, 其功能障碍可能影响个体对情绪刺激的认知评估和应对能力. 岛叶参与自我意识、内部感受和认知控制等过程, 其功能紊乱可能影响个体对情绪和身体感受的整合与调节能力. 研究表明, 前额叶和岛叶皮层在处理情感信息时存在显著的性别差异. 当面对情感信息刺激时, 女性前侧扣带回皮层和男性的左侧额下回(left inferior frontal gyrus)及前岛叶皮层有着更强的激活[17]. 此外, 男性和女性的皮层区域对正向和负向的情绪信息具有不同程度的反应. 男性的额叶回下部和内侧部对积极的情绪图片信息产生更强的反应, 而女性的前部和中部扣带回对负向信息的图片产生更强的激活[18]. 岛叶皮层的活动也具有两性差异的侧向异化特征[19]. 在回忆情绪事件时, 女性和男性激活的脑区有所差异. 女性在提取悲伤记忆期间, 双侧的扣带回皮层、前额叶皮层左内侧部以及岛叶皮层激活, 而男性只有左侧岛叶皮层和右侧尾状核(right caudate nucleus)有部分激活. 在回忆快乐事件时, 女性激活了右侧尾状核和左侧前扣带回皮层, 男性激活了右侧尾状核、左侧壳核(left putamen)和左侧额上回(left superior frontal gyrus), 且男性激活程度高于女性[20]. 这些性别差异可能与两性在情绪体验、表达和调节方面的差异有关, 也可能影响焦虑和抑郁障碍在两性中的发生、发展和临床表现.

直接针对焦虑和抑郁患者的脑成像研究揭示了情绪处理相关脑区的两性区别. 例如女性前扣带回皮层腹侧和后侧部在焦虑和抑郁当中的活动水平比男性更高[21]. 此外, 前扣带回皮层也是在焦虑和抑郁障碍患者中存在性别体积差异的脑区[22]. 单光子发射计算机断层扫描(single photon emission computed tomography, SPECT)和正电子发射计算机断层扫描(positron emission tomography, PET)等技术能揭示更细致的大脑性别差异特征. 通过这些方法, 研究者发现多巴胺(dopamine)和5-羟色胺(5-hydroxytryptamine, 5-HT)受体存在性别差异[23,24]. 在额叶和扣带回皮层中, 女性5-HT1A受体结合程度高于男性, 而5-HT2受体的结合程度则低于男性[25,26]. 脑成像研究证明了皮层区域在焦虑和抑郁障碍的性别差异中发挥着极为重要的作用, 为进一步理解焦虑和抑郁障碍的性别差异分子机制提供了重要的线索.

2 焦虑和抑郁障碍两性差异的分子机制探索

2.1 基于药物临床治疗的研究

当前广泛使用的抗抑郁药物对两性的疗效存在差异, 这从另一个角度揭示了焦虑和抑郁障碍发病机制的性别差异. 临床研究表明, 选择性5-HT重吸收抑制剂(SSRIs)类抗抑郁药物, 如舍曲林(sertraline)和西酞普

兰(citalopram), 对女性抑郁和焦虑障碍的缓解效果优于男性[27,28]. 相比之下, 三环类(TCAs)抗抑郁药物丙咪嗪(imipramine)对男女疗效相近[27]. TCAs类药物可抑制去甲肾上腺素(norepinephrine)和5-HT的重吸收, 而SSRIs类药物选择性抑制5-HT的重吸收. 此外, SSRIs类药物文拉法辛(venlafaxine)在老年女性中的疗效弱于年轻女性, 而男性则无年龄差异[29]. 这提示抗抑郁药物疗效的性别差异可能与性激素的作用有关. 5-HT受体在两性中的表达存在差异, 且受性激素调节[30~32]. 因此, 以5-HT系统为靶点的抗抑郁药物更有可能产生两性差异的治疗效果. 这些临床证据表明, 探索焦虑和抑郁障碍两性差异机制有助于开发更精细化的治疗策略. 然而, 目前关于抗抑郁药物疗效性别差异的机制尚不明确, 仍需在动物模型上开展进一步研究. 深入理解两性差异机制不仅有助于优化现有药物的临床应用, 也为开发新型性别特异性治疗方案提供了理论基础和实验依据.

2.2 雌雄两性动物模型研究进展

当下常见的焦虑和抑郁模型包括习得性无助(learned helpless)、生命早期应激(early life stress)、慢性社交挫败压力(chronic social defeat stress)、慢性束缚应激(chronic restraint stress)和不可预测慢性压力(unpredictable chronic mild stress)等[33]. 早期的焦虑和抑郁疾病模型通常局限于雄性实验动物, 而这些范式未必适用于雌性动物的研究, 这导致了人们对女性的发病机制了解甚少. 近年来人们逐步发展出多种雌性疾病模型的构造模式, 并将其应用于焦虑和抑郁疾病的两性差异机制的研究当中.

生命早期应激往往会增加成年后患焦虑和抑郁障碍等多种精神疾病的风险[34,35]. 常见的早期应激方式如母婴分离, 已在雌性动物当中有了较多的应用[36~39]. 经历母婴分离的雌性小鼠的社会行为和焦虑水平有所增加, 而雄性小鼠的运动和探索活动受到影响[40]. 另一种修改的早期应激方法是将小鼠的垫料替换成网格底部, 从而减少雌鼠的筑巢和哺育行为, 可诱导成年雌鼠表现出比雄鼠更明显的抑郁特征[41].

慢性社交挫败压力是在雄鼠当中常用的焦虑和抑郁造模方式. 短期的社交挫败压力可导致雄鼠焦虑水平的变化, 长期的压力可诱导社交回避、快感缺失和习得性无助等抑郁表型. 此前的社交挫败模型无法应用于雌鼠的缺陷在于, 雄鼠在自然状态下会对同性个体展现出攻击性, 而针对雌鼠的攻击行为则较难被诱导. 新近的研究不断优化了慢性社交挫败压力范式, 使其应用于雌鼠的研究. 虽然通常雄鼠不会对雌鼠展现攻击行为, 但是激活腹中侧下丘脑腹后侧部(ventrolateral subdivision of the ventromedial hypothalamus)可诱发雄鼠对雌鼠的攻击性, 诱导雌鼠产生社交回避和焦虑水平增高等表现[42]. 另一项研究发现, 单独与雄鼠配对饲养的Swiss Webster(CFW)雌鼠, 可对C57BL/6J 雌鼠表现出较强的攻击性. 由此可将雄性慢性社交挫败压力当中的攻击方替换为CFW雌鼠, 从而诱导C57BL/6J 雌鼠的本底焦虑水平增高以及社交回避等行为[43]. 另一种改进的建模方式称为可视化慢性社交挫败压力(vicarious chronic social defeat stress), 即小鼠可通过观察其他小鼠被攻击而产生应激反应, 同样可诱导雌鼠的抑郁样表现[44]. 还有研究者把目光投向了其他模式动物. 加利福尼亚鼠(*Peromyscus californicus*)的雄性和雌性个体都有捍卫领地的特点, 因此也存在雌性彼此间的攻击行为, 可用于雌性的社交挫败压力实验[45] (图1).

雌性动物模型的建立为深入阐明焦虑和抑郁障碍的性别差异发病机制奠定了重要基础. 未来对雌性动物模型的进一步优化, 并结合分子、细胞和神经环路水平的研究, 将有助于揭示雌雄动物在应激反应、情绪调节和社会行为等方面的差异, 为开发针对焦虑和抑郁障碍的性别差异的诊断和治疗策略提供科学依据.

2.3 遗传因素在焦虑和抑郁障碍中的性别差异作用

众所周知, 人类的性别由XY性染色体上的性别决定基因控制. 遗传关联性分析有助于我们寻找潜在的病理信息. 许多研究表明, 大脑的发育过程受到了性相关的遗传调控, 最终产生了大脑结构上的性别异质性. 早先关于两性群体的遗传度分析反映了焦虑和抑郁障碍的遗传因素差异[46~48]. 近年来关于抑郁障碍的遗传分析, 特别是全基因组关联性分析(genome-wide association studies, GWAS)取得了重大突破, 已发现了将近两百个风险位点和超过两百个候选基因, 为揭示焦虑和抑郁障碍两性差异的遗传因素提供了直接的证据[49,50]. 考虑到某些基因可能在两性当中发挥着截然不同的功能, 在分析过程中将性别因素作为分类标准会更有利于寻找疾病的相关位点[51,52]. 虽然近年来人们陆续发现了多个焦虑和抑郁相关的两性差异风险位点, 但是它们的功能机制还有待进一步的探索. 在更近

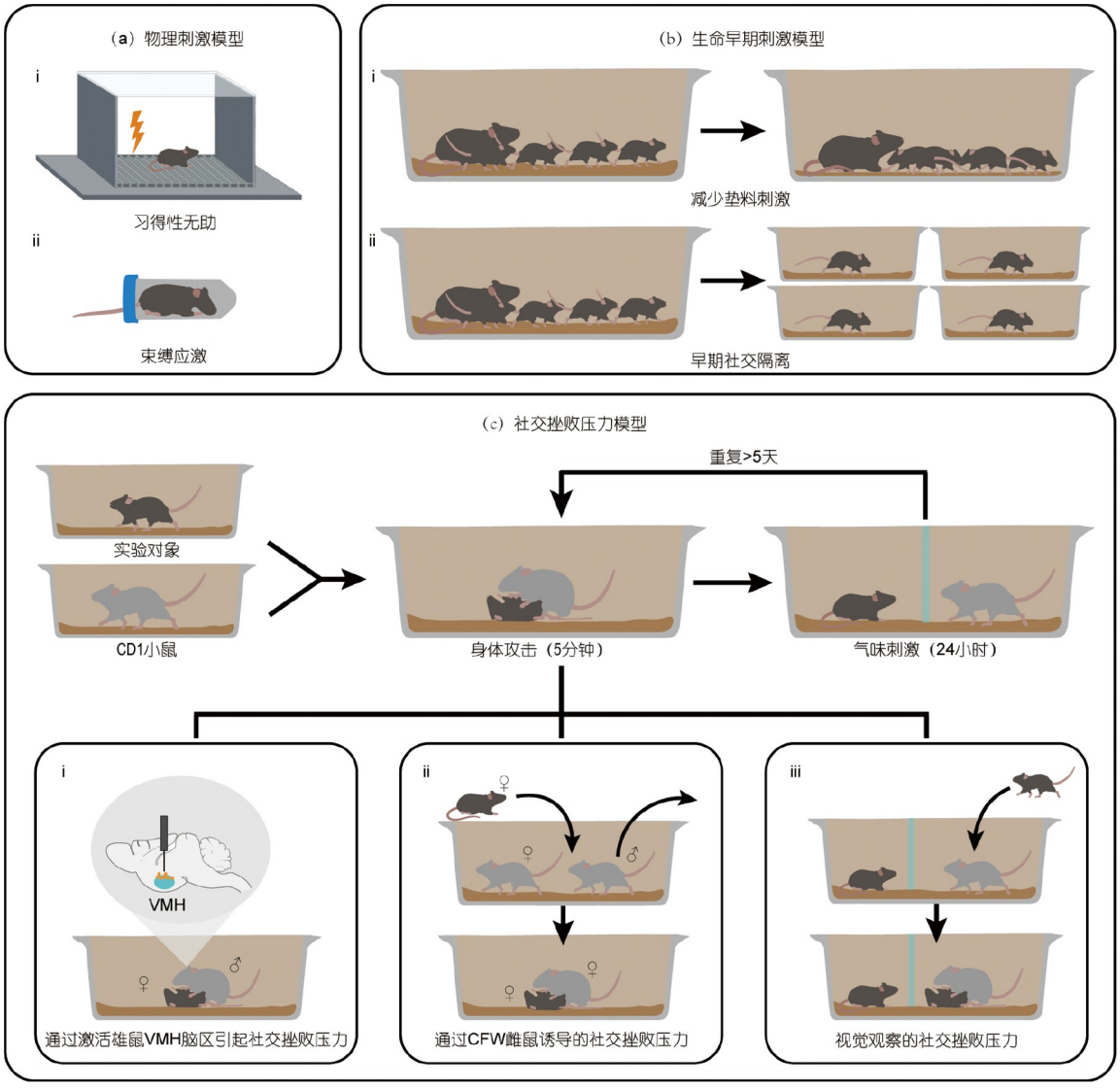

图 1 适用于两性的应激动物模型. (a) 物理刺激模型. 足底电击(i)和将小鼠束缚于狭窄空间(ii)是两种对小鼠产生应激的方式. 若雄鼠和雌鼠反复经历多次无法逃避的电击或束缚刺激, 可产生习得性无助的抑郁样表型. (b) 生命早期刺激模型. (i) 移去笼子底部的垫料可减少雌鼠的筑巢和哺育行为, 从而对雄鼠和雌鼠的后天行为产生永久性影响. (ii) 在早期发育阶段对雄鼠和雌鼠的社交隔离可诱导后天的社交行为及本底焦虑水平等发生改变. (c) 社交挫败压力模型. 在典型的雄性小鼠社交挫败压力模型当中, 实验对象每天被引入不同的CD1小鼠饲养笼内, 经历5分钟左右的攻击. 在剩余时间里, 实验对象被有孔的透明插板隔开, 但依然可接受来自CD1小鼠的气味和视觉刺激. 该过程通常需要重复5 d以上从而诱导实验对象的焦虑和抑郁表现. 目前在雌性小鼠的社交挫败压力模型当中, 人们可通过激活腹中侧下丘脑(ventromedial hypothalamus, VMH)来诱导雄性CD1小鼠对雌鼠的攻击(i); 或将配对饲养的Swiss Webster(CFW)雄鼠暂时移开, CFW雌鼠可对引入的实验对象表现出攻击性(ii). 雌鼠通过视觉观察其他小鼠遭受攻击的方式也可产生焦虑反应(iii)(部分素材来自BioRender.com)

Figure 1 Stress animal models applicable to both sexes. (a) Physical stress models. (i) Electric foot shock and (ii) restraint of mice in a narrow space are two methods used to induce stress in mice. Both male and female mice repeatedly experiencing inescapable foot shocks or restraint stress may develop a learned helpless phenotype resembling depression. (b) Early life stress models. (i) Removal of home cage bedding reduces nesting and parenting behaviors in females, leading to permanent changes in the behavior of offspring. (ii) Social isolation of male and female mice during early developmental stages can induce changes in social behaviors and basal stress levels in adulthood. (c) Social defeat stress models. In the classic model for male mice, experimental subjects are introduced into the home cage of different CD1 mice daily, where they are physically attacked by CD1 males for approximately 5 min. For the remaining time, experimental subjects are separated by a transparent perforated divider, allowing continuous exposure to olfactory and visual stimuli from CD1 males. This procedure is typically repeated for more than 5 days to induce anxiety and depression-like behaviors. In the social defeat stress model for females, three variations exist: (i) manually stimulating the ventromedial hypothalamus (VMH) of CD1 males to induce attacks on female subjects; (ii) temporarily removing the male from pair-housed Swiss Webster (CFW) mice, causing the CFW female to attack the introduced female subject; and (iii) exposing female subjects to visual observation of other mice being physically attacked, which can induce stress responses (Some components sourced from BioRender.com)

的研究当中，研究者对更大规模的UK Biobank约27万人的全基因组数据的分析，分别在女性和男性群体当中找出了11个和1个相关的染色体位点，以及64和53个风险基因[53]. 进一步针对风险基因富集的信号通路揭示了两性差异的调控机制：男性抑郁障碍患者的风险基因与表观遗传调控有关，特别是组蛋白的编码；女性抑郁障碍患者的风险基因与轴突蛋白(neurexin)、多巴胺受体D2(dopamine receptor D2, DRD2)和代谢型谷氨酸受体5(metabotropic glutamate receptor 5, mGluR5)的关系密切[53]. 此外，该项研究还发现部分风险基因与代谢指标有显著关联，且只在女性当中高度相关，这印证了女性抑郁障碍患者出现的暴食现象[53].

遗传因素对焦虑和抑郁障碍的发病有着相当的贡献，但其病因更多来自环境因素，例如后天的生活条件、教育方式、工作压力和文化特征等. 当前研究者常用的焦虑和抑郁模型，例如社交挫败压力、习得性无助、早期应激压力、持续性束缚应激和不可预测压力等模型，核心的思路是模拟引起焦虑和抑郁障碍的环境. 这些环境因素一般不会直接改变基因组的序列，而是通过表观遗传的调控方式发挥作用，即在不改变基因组序列的情况下改变染色质的结构，从而调节基因的表达水平[54]. 目前已知的表观遗传调控方式有DNA甲基化修饰、组蛋白水平的修饰以及非编码RNA作用等. 在多项研究当中，人们逐步探索了焦虑和抑郁障碍的表观遗传变化.

许多关于焦虑和抑郁障碍表观遗传调控的研究关注发育阶段应激带来的成年后效应，例如本底焦虑水平的提升以及患抑郁障碍风险的增加[35]. 大脑的奖赏环路是焦虑和抑郁障碍患者当中活动异常的区域，其中伏隔核(nucleus accumbens)参与奖赏信息的编码，对于抑郁障碍当中的快感缺失现象有着重要作用[55,56]. 早先的研究发现，社交挫败压力可增加雄鼠伏隔核的DNA甲基转移酶3a(DNA methyltransferase 3a, Dnmt3a)的表达，在伏隔核抑制或过表达Dnmt3a可分别减轻或增强雄鼠的抑郁表现[57]. 在一种慢性不可预测焦虑模型中，雌鼠在持续6 d的应激过后展现出抑郁特征，伴随着伏隔核的转录水平变化. 在伏隔核特异敲除Dnmt3a使雌鼠转录组水平与雄鼠更为接近，并增强了雌鼠的应激抗性[58]. 人群样本的证据也支持抑郁障碍的表观遗传两性差异. 研究者对老年重性抑郁障碍(major depressive disorder)患者的前额叶皮层采样发现，若干基因的甲基化水平与重性抑郁障碍相关且存在两性差异，包括*YOD1*、*PRICKLE4*、*GFAP*、*RP11-1E3.1*和 *UBB* 在内的基因仅在男性患者当中有显著的关联[59].

长非编码RNA(long non-coding RNAs, lncRNAs)是一种特殊的表观遗传调控RNA. lncRNAs通常包含超过200个核苷酸，与蛋白编码基因的碱基序列类似. lncRNAs的功能包括RNA干扰调节基因的表达或剪切、直接结合蛋白质调节其活性，以及作为核酸蛋白质复合体的成分等. 在抑郁障碍患者人脑转录组数据库当中，大约30%的抑郁障碍患者表达差异基因为lncRNAs[60]. 其中一个长非编码RNA LINC00473在女性患者的前额叶皮层表达下降，而在男性患者中没有变化. 在小鼠前额叶皮层表达LINC00473能够模拟人类的两性差异特征，提升了雌鼠对抑郁的抗性[61]. 在大鼠模型的研究中发现，有无习得性无助表型的霍尔茨曼大鼠(Holtzman rat)lncRNAs的表达具有明显差异；而经抗抑郁药物氟西汀(fluoxetine)治疗过后，抑郁样大鼠的lncRNAs表达得到恢复[62]. 这些发现提示lncRNAs可能在抑郁障碍的性别特异性发病机制以及抗抑郁治疗中发挥重要作用.

转录组分析揭示了两性之间基因表达水平的巨大差异. 对抑郁障碍患者前额叶皮层和前脑岛等相关脑区组织的转录组分析表明，两性患者异常表达基因差异极大，仅有5%~10%的重合[60]. 其中*DUSP6*和*EMX1*分别在女性和男性患者的表达网络中占据核心位置. 在小鼠前额叶皮层抑制*Dusp6*基因的表达，可诱导雌鼠而非雄鼠的抑郁样表型[60]. 另一项基于抑郁障碍患者尸检的研究中，研究者发现女性抑郁障碍患者前额叶皮层背外侧部的多个谷氨酸系统相关基因表达显著上调，尤其在抑郁导致自杀的患者中更为明显[63]. 基因的表达离不开遗传和表观遗传的调控，两性转录组水平的显著区别也是遗传和表观遗传差异的直接体现.

关于焦虑和抑郁障碍在遗传和表观遗传的研究初步揭示了潜在的两性差异机制. 当前通过全基因组筛查发现的许多基因也参与到了表观遗传的调控当中，这说明遗传和表观遗传因素并非相互独立的，可能共同参与构成了精神疾病的性别差异病理基础. 当前筛选出的遗传和表观遗传风险位点还有待动物模型的验证，以及与已知的焦虑和抑郁障碍机制相联系. 这将有助于揭示新的病理机制，为开辟新的治疗策略提供思路.

2.4 性激素在焦虑和抑郁障碍中的性别差异作用

性激素主要包含雌激素(estrogens)、孕酮(progestone)和雄激素(androgens)三类甾体激素[64]. 在早期发育阶段, 激素系统对于神经系统的性别特征形成发挥着重要的作用, 调节特定脑区的神经细胞数量以及脑区之间的连接强度; 在成年阶段, 激素系统维持着两性特征从而产生不同的行为表现[65~69]. 激素系统调节多种神经递质的释放, 包含谷氨酸、γ-氨基丁酸(γ-aminobutyric acid, GABA)、多巴胺和5-HT等[70,71]. 性激素受体在杏仁核、终纹床核(bed nucleus of the stria terminalis, BNST)、下丘脑、额叶皮层和海马等焦虑和抑郁相关脑区当中具有很高的表达水平[72~74]. 此外, 在雌性动物体内还存在动情周期以及孕期相关的激素水平波动, 对行为的调节发挥着不可忽视的作用.

女性抑郁障碍发病率约为男性的两倍, 且这种差异在青春期至更年期之间最为显著, 可能与月经周期的激素水平波动有关[75]. 绝经前期激素水平的不稳定变化, 会增加抑郁障碍的风险[76,77]. 女性激素水平周期性变化也可能影响焦虑和抑郁的程度, 约三分之二的女性重性抑郁障碍患者报告在月经前期病症加重[78]. 产后抑郁症(postpartum depression)是另一种特殊的抑郁形式, 发病率约为17%, 与产后雌激素和孕酮水平的急剧下降密切相关. 尽管许多研究报道了成年动物在应激反应下的性别差异, 但在发育期动物中未观察到焦虑和抑郁的雌雄区别, 这可能与性激素介导的大脑功能差异尚未充分建立有关[79,80].

性激素对焦虑和抑郁障碍发病机制的作用已有大量研究. 雌激素可调节5-HT系统, 补充雌激素可增加前额叶皮层等多个区域的5-HT2A受体水平[81~84]. 小鼠多个表达性激素受体的脑区存在结构性别差异, 而雌甾二醇类激素是大脑中调节性分化和本能性行为的主要激素. 例如雄鼠终纹床核后部(posterior BNST, BNSTp)脑区比雌鼠有更大的体积、不同的基因表达特征和更多的Nfix和Tac2标记细胞. 这些差异需要ERα(oestrogen receptor-α, ERα)受体的维持. 敲除ERα受体后, 雄鼠BNSTp脑区便失去了基因表达的差异性[85].

产后抑郁与孕酮及其代谢物四氢孕酮水平变化密切相关. 怀孕期间, 孕酮和四氢孕酮水平逐渐升高, 但在分娩后急剧下降[86,87], 这种激素水平的骤然变化可能是导致部分产妇出现抑郁症状的原因之一. 四氢孕酮具有抗焦虑和抗抑郁作用[88], 其水平下降可能使产妇更易出现情绪问题. 在大鼠模型中, 给予孕酮并戒断可诱导抑郁样症状, 且氟西汀和度洛西汀(duloxetine)对该动物模型的抑郁表型治疗效果不佳, 但三环类药物阿米替林(amitriptyline)有一定疗效, 这提示产后抑郁与其他类型的抑郁障碍可能存在不同的病理机制[89]. 四氢孕酮可直接作用于GABA A型受体[90], 其中δ亚基与甾类激素作用最为显著. 敲除δ亚基可减少四氢孕酮戒断引起的焦虑反应[87]. 另一研究发现, 雌激素调节内侧视前区(medial preoptic area, MPOA)GABA能(GABAergic)神经元活动并影响多种抑郁表型, 该群神经元至腹侧被盖区(ventral tegmental area)和中缝背核(dorsal raphe nucleus)的投射, 分别调节快感缺失和习得性无助的抑郁特征[91].

临床上, 改变性激素的水平可对焦虑和抑郁障碍达到一定的治疗效果. 亮丙瑞林(leuprolide)是一种类似促性腺激素的激动剂, 可缓解月经前期的焦虑症状[92]. 绝经期激素替代疗法(menopausal hormone therapy)可通过补充雌激素来改善绝经后女性的焦虑和抑郁程度[93]. 而在绝经期治疗过后停止服用雌激素, 会增加抑郁障碍复发风险[94].

综上所述, 月经周期、绝经期和围产期的激素波动与女性焦虑和抑郁障碍的高发病率密切相关. 性激素通过调节神经系统发育、神经递质释放和特定脑区活动等多种机制, 在焦虑和抑郁障碍的性别差异中发挥着关键作用. 深入研究性激素与焦虑和抑郁障碍的关系, 对于理解和治疗女性焦虑和抑郁障碍具有重要意义.

2.5 神经肽在焦虑和抑郁障碍中的性别差异作用

神经肽是由神经元合成并释放的小分子肽类物质, 在神经系统中发挥着调制功能[95]. 目前已知与焦虑和抑郁障碍两性差异密切相关的神经肽包括促肾上腺皮质激素释放激素(corticotropin-releasing factor, CRF)、催产素(oxytocin)、神经肽Y(neuropeptide Y, NPY)和血管加压素(vasopressin)等. 这些神经肽及其受体在焦虑和抑郁障碍相关脑区具有较高水平的表达, 动物模型中的研究也显示它们的功能存在明显的两性差异特征.

CRF主要由下丘脑室旁核(paraventricular nucleus of the hypothalamus, PVN)分泌, 通过下丘脑-垂体-肾上腺轴(hypothalamic–pituitary–adrenal axis, HPA轴)调节应激反应, 在焦虑和抑郁障碍中发挥关键作用. 焦虑和抑郁障碍患者的HPA轴时常处于持续激活的状态,

且HPA轴的激活程度存在两性差异. 研究表明, 经历相同束缚应激时, 雌性大鼠的PVN、BNST腹前区和MPOA的CRF表达量高于雄性大鼠[81], 这提示CRF在应激条件下的释放存在两性差异. 此外, 早期社交隔离应激可导致雌鼠CRF释放神经元兴奋性减弱, 而雄鼠无此改变[96]. CRF与受体结合还受CRF结合蛋白(CRF binding protein, CRF-BP)调节, CRF-BP表达不足可能导致产前焦虑[97]. 在慢性不可预测应激模型中, 雌鼠的伏隔核CRF信号通路改变幅度大于雄鼠, 可能是雌性更易焦虑的原因之一[58]. 雌鼠终纹床核卵圆形核(oval nucleus of bed nuclei of the stria terminalis, ovBNST)内释放CRF的神经元比雄鼠更容易被应激压力激活, 这也是介导雌鼠更易产生焦虑样行为的重要细胞和环路机制[98].

蓝斑核(locus coeruleus, LC)高表达CRF受体, 释放去甲肾上腺素并广泛投射至多个脑区, 参与觉醒和注意力的调节, 与抑郁障碍的警觉过度症状有关[99]. 激活雌鼠的LC脑区CRF受体可引起神经元更强烈的发放[100,101]. 进一步研究发现这主要是由LC区域CRF受体下游通路的两性差异引起的. 雌性大鼠的CRF受体与G蛋白偶联受体Gs的结合更多, 从而对下游AMP-PKA通路的激活更强; 雄性大鼠LC的CRF受体结合更多的β-arrestin, 当CRF受体持续激活时可介导受体的内吞, 减少神经元的活动[101]. 然而, CRF系统在不同脑区表现出性别特异性的作用方式. 例如, 在前额叶皮层, CRF对雄性大鼠2/3层锥体神经元的激活程度高于雌性[102]. 这提示CRF系统在调控情绪和认知功能的神经环路中, 可能存在更为复杂的性别差异机制. 鉴于CRF系统在焦虑和抑郁症状中的核心作用, 其已成为治疗策略开发的重要方向之一. 深入研究CRF系统在不同脑区和神经环路中的性别差异表达和调控模式, 将有助于全面理解其在焦虑和抑郁障碍性别差异中的作用.

催产素主要由下丘脑PVN和视交叉上核(supraoptic nucleus)释放, 对社交、焦虑、摄食和繁殖发挥着重要的调节功能. 催产素的受体表达具有两性差异, 例如在大鼠的研究当中, 雄性大鼠的BNST、PVN等焦虑和抑郁障碍相关脑区的催产素受体表达高于雌性; 雌性大鼠在外侧隔核(lateral septum, LS)中间部、前颗粒状岛叶皮层(anterior agranular insular cortex)等脑区当中的催产素受体表达高于雄性[103]. 前额叶皮层具有一群表达催产素受体的抑制性神经元存在两性差异调控作用, 抑制该群神经元或者添加催产素受体拮抗剂仅影响了发情期的雌鼠对异性的社交偏好[104]. 而在雄鼠当中, 该群神经元可通过释放CRF-BP抑制CRF和2/3层椎体神经元的结合, 从而在雄性当中起到抗焦虑的作用[102]. 在应对社交压力时, 向受试者鼻腔施加催产素的效果也表现出两性差异. 男性受试者在接受催产素之后表现为负面情绪减少, 但是女性受试者接受催产素后的负面情绪并未显著改善, 甚至更易表现出愤怒情绪[105].

NPY系统对焦虑和抑郁行为起到重要的调节作用, 并具有两性差异特征. 临床上抑郁障碍患者前额叶皮层和海马的NPY表达水平下降, 其受体NPY1R和NPY2R的表达水平上升, 提示NPY与抑郁障碍有着紧密的相关性[106]. NPY对焦虑和抑郁的调节在动物模型当中已有充分的验证, 向体内给予NPY及其类似物起到抗焦虑的作用[107~111], 而敲除NPY则使焦虑水平增加且伴有抑郁表型[112,113]. 在大鼠当中, 具有抑郁表型雌鼠和雄鼠的NPY释放量均下降[114,115], 且无论是对照还是抑郁组的雌性大鼠释放量都低于雄性[115]. 多项研究报道了在下丘脑、海马和纹状体当中, 雄性的NPY表达高于雌性[116~119]. 这提示雌性动物NPY系统的功能相对较弱, 可能是其更易患焦虑和抑郁障碍的原因之一.

由于NPY的表达受到雌激素的调节, 因此NPY在雌性中的抗焦虑效果会发生波动. 下丘脑的NPY神经元表达雌激素受体ERα, 在雌激素作用下NPY的释放减少[120]. 由此NPY的水平也会随着发情周期而波动, 在大鼠的发情前期(proestrus)NPY的表达量要高于发情间期(metestrus)[121]. 这种波动反映在NPY的抗焦虑效果上: 向大鼠LS脑区给予NPY可起到抗焦虑作用, 但在发情间期所需的剂量要高于发情前期, 说明NPY对焦虑和抑郁障碍的调节随着本底激素水平而改变[122]. 此外, NPY也参与食物摄入的调节, 且女性抑郁障碍患者更易具有暴食的特征[123,124]. NPY的抗焦虑和抑郁效果, 以及NPY系统在两性中的表达差别, 在一定程度上解释了焦虑和抑郁的两性易感性差异, 而NPY随着激素水平的波动很可能解释了焦虑和抑郁障碍状与月经周期的关联性.

血管加压素具有抗焦虑的作用, 主要在PVN脑区表达. 特异敲除PVN的血管加压素编码基因可导致雌雄不同的行为变化. 其中雌鼠对同性和异性的社交探索增加, 但是雄鼠的焦虑水平上升[125]. 此外, 下丘脑血管加压素释放神经元的投射密度也存在两性差异. 在BNST、LS等多个焦虑相关脑区当中, 雄鼠的血管加压

素神经元投射密度更高[126,127]. 在LS脑区当中, 雌性大鼠表达更多的血管加压素受体V1a[103,128]. 当性腺被切除之后, 大部分脑区的血管加压素神经元投射密度下降, 且两性差异消失, 说明这种投射受到外周激素水平的维持[129](图2).

总之, 神经肽在焦虑和抑郁障碍中的性别差异作用涉及多个脑区和神经环路, 并受到性激素等因素的调控. 深入研究这些神经肽系统在不同脑区和神经环路中的性别差异表达和调控模式, 将有助于全面理解其在焦虑和抑郁障碍性别差异中的作用机制, 为开发性别特异性的诊断和治疗策略提供重要线索.

3 焦虑和抑郁障碍的区别及其两性差异的联系

焦虑和抑郁障碍往往相互关联. 世界卫生组织的调查表明, 约45%的重度抑郁障碍患者经历过某种焦虑障碍[129]. 在我国的一项调查当中, 约55%的抑郁患者同时报告有焦虑症状, 另外约47%的焦虑障碍患者报告有抑郁症状[130]. 焦虑障碍被认为是抑郁障碍的主要风险因素之一[131]. 焦虑和抑郁障碍的区别在于, 焦虑和恐惧往往是对未来的不确定因素和临近的威胁产生的反应[132,133]; 而抑郁可被认为与对过去事件的不良记忆有关, 包括正向记忆的缺损和负向记忆的增强, 由

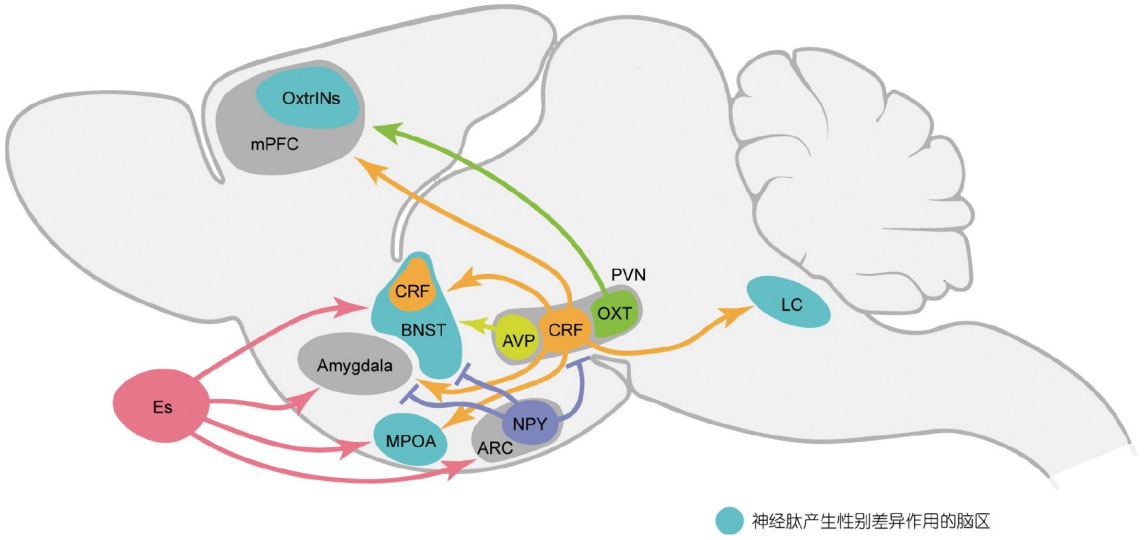

图 2 已知参与焦虑和抑郁调节并具有两性差异的鼠脑区域. 来自PVN的OXT和CRF作用于前额叶皮层中部(medial prefrontal cortex, mPFC). 前额叶皮层中部表达OXT受体的中间神经元调节雌鼠动情期特异的异性社交行为, 在雄鼠当中则对焦虑行为发挥更强的调节作用. CRF还作用于杏仁核、LC、MPOA和BNST等焦虑和抑郁相关脑区. 其中雌鼠的LC区域对CRF更敏感. 血管加压素和NPY系统也具有两性差异特征, 血管加压素作用于BNST; NPY作用于杏仁核、BNST以及下丘脑室旁核, 对CRF起到一定的拮抗作用. 此外, 这些焦虑和抑郁障碍相关脑区大多表达雌激素的受体, 受到外周性激素的调节. BNST与MPOA具有明显的结构和功能的两性差异. 雄性的BNST具有更大的体积; 雌性的MPOA接受外周激素的调节, 从而介导了外周激素水平波动导致的焦虑和抑郁. (Amygdala 杏仁核; ARC: Arcuate nucleus 弓状核; AVP: Arginine vasopressin 血管加压素; BNST: Bed nucleus of the stria terminalis 终纹床核; CRF: Corticotropin-releasing factor 促肾上腺皮质激素释放激素; Es: Estrogens 雌激素; LC: Locus coeruleus 蓝斑核; mPFC: Medial prefrontal cortex 前额叶皮层中部; MPOA: Medial preoptic area 内侧视前区; NPY: Neuropeptide Y 神经肽Y; OXT: Oxytocin 催产素; OxtrINs: Oxytocin receptor interneurons 催产素受体中间神经元; PVN: Paraventricular nucleus of the hypothalamus 下丘脑室旁核)(部分素材来自BioRender.com)

Figure 2 Sexually dimorphic regions in the mouse brain involved in regulating anxiety and depressive disorders. Oxytocin (OXT) and corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus (PVN) innervate the medial prefrontal cortex (mPFC). In females, OXT receptor-expressing interneurons (OxtrINs) in the mPFC modulate estrous cycle-specific social behavior, while in males, they exert a more pronounced effect on anxiety behaviors. CRF also innervates various brain regions associated with anxiety and depressive disorders, including the locus coeruleus (LC), amygdala, medial preoptic area (MPOA), and bed nucleus of the stria terminalis (BNST). Notably, the female LC is more sensitive to CRF. The arginine vasopressin (AVP) and neuropeptide Y (NPY) systems also exhibit sexually dimorphic characteristics. AVP regulates the BNST, while NPY functions in the amygdala, BNST, and PVN, antagonizing CRF effects. Additionally, most anxiety and depressive disorder-associated brain regions express estrogen (Es) receptors, which are influenced by peripheral sex hormones. The BNST and MPOA display distinct sexual dimorphism in structure and function. The male BNST generally has a larger volume, while the female MPOA is regulated by peripheral sex hormones, mediating anxiety and depressive disorders caused by fluctuations in peripheral sex hormone levels. ARC: arcuate nucleus; AVP: arginine vasopressin; BNST: bed nucleus of the stria terminalis; CRF: corticotropin-releasing factor; Es: estrogens; LC: locus coeruleus; mPFC: medial prefrontal cortex; MPOA: medial preoptic area; NPY: neuropeptide Y; OXT: oxytocin; OxtrINs: oxytocin receptor interneurons; PVN: paraventricular nucleus of the hypothalamus (Some components sourced from BioRender.com)

此引起对自我和环境的过度消极应对[134,135]. 从神经活动的角度来看, 焦虑和抑郁障碍当中活动异常的脑区有一定程度的重叠. 这些共同的区域包括HPA轴相关的脑区, 情绪处理相关的杏仁核和前额叶皮层, 以及蓝斑核为代表的调节觉醒的脑区等[136,137]. 这些脑区大多存在两性差异的特征, 从而在焦虑和抑郁障碍的发病过程中产生近似的影响, 表现为两类精神障碍的女性发病率和严重程度高于男性. 当前多数研究证据支持女性在面对压力时产生更强的应激反应. 在动物焦虑模型当中, 人们能够稳定地观察到雌性动物应激时HPA轴相较于雄性产生更强的激活[81,138~142]. 在蓝斑核当中, 雌性小鼠的神经元对CRF的反应要强于雄鼠[100,101]; 在BNST区域, 雌性小鼠释放CRF的神经元在应激状态下表现出过度的兴奋[98]. 此外, CRF系统与催产素、NPY等神经调制系统也存在紧密的联系, 而这些神经调制系统本身也具有两性差异的特征[102,107~111,143]. 女性CRF系统更强的激活程度或许也解释了脑成像研究的现象, 例如女性在面对负性的信息以及提取负性记忆的时候, 杏仁核等情绪调控脑区的活动高于男性[18,20]. 在面对应激压力时, 女性大脑中与焦虑相关的脑区活动更强. 这些脑区长期处于高活动状态, 可能会导致其发生不可逆的功能或结构变化. 而这些与焦虑相关的脑区, 与抑郁障碍相关的脑区高度重叠. 因此, 女性中与应激相关脑区的异常改变, 可能既是焦虑障碍, 也是抑郁障碍性别差异的神经基础. 这种异常改变使得女性更容易发生严重程度更高的抑郁障碍. 综上所述, 具有性别差异的、应激相关脑区或分子功能的异常, 可能是焦虑和抑郁障碍在不同性别中发病率和严重程度差异的根本原因.

4 总结

焦虑障碍和抑郁障碍具有显著的性别差异, 且女性患病率明显高于男性. 探究其中的性别差异机制, 对于更好地理解其病理机制, 制定性别特异性诊疗策略, 改善患者预后具有重要意义. 雌性特异性的疾病动物模型的建立, 如母婴分离和改良的慢性社交挫败应激等, 为探究性别差异的环路和行为机制提供了有力工具. 当前的研究已从流行病学、脑成像、动物模型、分子和细胞机制等多个层面揭示了其中的性别差异. 人群研究表明情绪相关脑区在活动水平、功能连接以及对药物的反应性等方面存在显著的性别差异. 此外, 遗传和表观遗传学分析揭示了两性在基因表达调控、信号通路等方面的差异. 神经递质, 尤其是5-HT系统, 以及性激素如雌激素等对相关神经环路的性别特异性调控, 也是导致发病机制和治疗效果具有性别差异的重要因素. 尽管当前研究取得了一些进展, 但我们对介导两性差异的焦虑和抑郁障碍神经机制仍了解有限. 目前针对女性焦虑和抑郁障碍患者的研究尚不充分. 神经科学研究中包含女性群体或雌性动物样本的比例较低[144,145], 药物临床研究中对女性的评估尚存不足[146]. 雌性模式动物的应用还涉及到发情周期的变化, 然而人们关于发情周期对雌鼠神经活动影响的研究仍然缺乏. 当前已有初步的关于焦虑和抑郁障碍患者两性差异的基因组和转录组水平分析, 但是两性差异表达的基因如何发挥功能, 以及是如何在疾病情况下被异常调控仍不清楚. 近年来, 研究者开发了多种适用于雌性的焦虑和抑郁模型, 这将有利于建立精细化的性别特异性疾病模型, 推动焦虑和抑郁障碍性别差异发病机制的研究. 基于性别差异机制的探索, 有望发现性别特异性的诊断生物标志物, 包括脑成像、外周生物标志物等. 针对性别差异的神经环路、细胞和分子机制的深入研究, 将为焦虑和抑郁障碍的精准治疗提供新的思路和靶点.

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Summary for “焦虑和抑郁障碍的性别差异神经机制”

Neural mechanisms underlying sex differences in anxiety and depressive disorders

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Anxiety and depressive disorders are prevalent mental health conditions that significantly burden individuals and society. Notably, these disorders exhibit substantial sex differences, with women showing a markedly higher prevalence and more severe symptoms compared to men. However, the neural mechanisms underlying these sex differences remain poorly understood. This review summarizes recent findings from human and animal studies that illuminate the sex-specific neural underpinnings of anxiety and depressive disorders.

Neuroimaging studies in human populations have revealed sex differences in the activation and functional connectivity of brain regions implicated in emotion processing and regulation, such as the amygdala, prefrontal cortex, and insular cortex. Women exhibit heightened amygdala reactivity to negative emotional stimuli and greater activation of the anterior cingulate cortex in anxiety and depressive disorders. In contrast, men show stronger amygdala-prefrontal connectivity and activation of the left inferior frontal gyrus and anterior insula in response to emotional information. Sex differences in neurotransmitter systems, particularly serotonin and dopamine, have also been observed in the frontal and cingulate cortices. Clinical pharmacological research suggests that antidepressants targeting the serotonin system may contribute to sex differences in treatment efficacy. Moreover, genetic and epigenetic analyses have identified sexually dimorphic risk loci and genes involved in processes such as DNA methylation and long non-coding RNA modulation, which may contribute to the sex differences in these disorders.

Studies using animal models have provided valuable insights into the molecular and cellular mechanisms underlying sex differences in anxiety and depressive disorders. Traditional models, such as learned helplessness, early life stress, and chronic social defeat stress, have been largely limited to male animals. However, recent efforts have focused on developing and optimizing these paradigms for female animals. Modified early life stress protocols and chronic social defeat stress models have been successfully employed to induce anxiety- and depression-like behaviors in female rodents. These advancements have paved the way for investigating sex-specific mechanisms of anxiety and depression at the molecular, cellular, and neural circuit levels.

Sex hormones and neuropeptides play a crucial role in the observed sex differences in anxiety and depressive disorders. Sex hormones are essential for establishing and maintaining sexually dimorphic neural circuits. Estrogens, progesterone, and androgens regulate neurotransmitter release, and their receptors are widely distributed among brain regions implicated in anxiety and depressive disorders. Fluctuations in sex hormones, particularly during specific phases of the menstrual cycle, pregnancy, and menopause, have been associated with an increased risk of developing anxiety and depressive disorders. Neuropeptides, including corticotropin-releasing factor, oxytocin, neuropeptide Y, and vasopressin, exhibit sex differences and are involved in stress regulation, contributing to the sexual dimorphism in anxiety and depressive disorders.

In conclusion, current studies have highlighted significant sex disparities in anxiety and depressive disorders. However, our understanding of the neural mechanisms underlying these sex differences remains limited. Few studies include females, and clinical research still lacks comprehensive evaluation of treatments for women. Although many genetic loci and genes associated with sex differences in anxiety and depressive disorders have been identified, their functions are poorly understood. Future research integrating molecular, cellular, circuit, and behavioral levels will deepen our understanding of the mechanisms underlying these sex differences, facilitating the development of sex-specific diagnostic and therapeutic strategies.

sex difference, anxiety, depression, affective disorders

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