

中国生物精神病学研究近期进展之选择回顾

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摘要

通过查阅中国期刊全文数据库 (CNKI) 及美国国立医学图书馆生物医学文献数据库 (PubMed) 2003-2009年发表的与精神疾病如精神分裂症、抑郁症、双相情感障碍、强迫症、焦虑症及阿尔茨默氏病的相关研究文献, 从分子遗传学、神经内分泌免疫学、电生理学和神经药理学四方面概述现阶段中国生物精神病学研究进展。无论从动物模型还是临床患者, 从采用分子遗传学、还是神经生化、电生理学或神经药理学方法, 都从不同角度对多种精神疾病的发病机理及治疗进行了广泛研究。

关键词: 生物精神病学、中国、研究进展

前言

生物精神病学作为精神病学的分支之一, 主要围绕精神疾病的分子遗传、神经生化、精神药理及神经免疫等方面探讨其病因、发病机制、治疗及预后。20世纪50年代初期Bennett^[1]最早提出「生物精神病学」的概念并撰文在《美国精神病学杂志》发表。随后第一个抗精神病药物氯丙嗪、抗抑郁药异丙烟肼和米帕明的出现, 促进了精神分裂症多巴胺假说和抑郁症单胺假说的建立, 从而奠定了现代生物精神病学的理论基础。近20年来, 生物精神病学的研究汗牛充栋, 其中分子遗传学和神经影像学技术在精神病学中的应用, 更促进了生物精神病学的发展, 为揭示精神疾病的病因及发病机制提供了科学的理论根据。本文就目前中国在该领域的研究进展作一综述。

分子遗传学

精神疾病的遗传学研究一直是生物精神病学的研究热点。经典遗传学研究如家系研究、寄养子研究、双生子研究已证实精神分裂症、双相情感障碍和抑郁症等均为遗传异质性多基因疾病。然而, 寻找多个微效疾病易感基因并非易事。全基因组扫描和候选基因研究仍是目前常用的遗传学策略。全基因组扫描是采用复盖整个基因组的DNA遗传标记, 以较大间距 (10-20 cM) 对大样本量的精神分裂症家系或同胞进行全基因组扫描, 通过遗传连锁分析将疾病相关基因定位在某一染色体区域, 在此基础上高密度地选择遗传标记 (约10 kb) 做精细分析, 进一步缩小定位区域, 最终确定疾病易感基因。候选基因策略是直接研究与疾病假说有关的基因, 分析这些候选基因的等位基因频率及单倍型在患病群体和正常群体之间的差异。前者的优势在于包含了所有与疾病相关的已知或未知的生物学机制, 但精确定位仍十分困难。后者则能直接地

阐明该基因在疾病中所起的作用及与之相关的疾病发生机制。全基因组扫描采用连锁分析, 候选基因策略采用关联分析。国内目前应用最广泛的是候选基因策略中的关联分析法。其中又以病例对照最为常用, 家系研究则较少。这与其操作简便、费用低廉有关。候选基因主要涉及多巴胺假说、5-羟色胺假说、谷氨酸假说和神经发育假说等。如最新几项研究分别探讨了多巴胺受体2基因^[2]、断裂基因 (*DISC1*)^[3]、前列腺素受体3基因 (*PTGER3*)^[4]、谷氨酸-半胱氨酸连接酶修饰亚单位基因^[5]、5-羟色胺6受体基因^[6]多态性与精神分裂症的关联、色氨酸羟化酶^[7]、突触回蛋白1及突触蛋白I基因^[8]多态与双相情感障碍的关联, 以及脑源性神经营养因子 (*BDNF*) 及糖原合酶 (*GSK3B*)^[9]基因多态与抑郁症的关联。其中尤为突出的是上海交通大学Bio-X中心研究组系统地研究了中国汉族精神分裂症的多个遗传易感基因如*FXR1*^[10]、早期生长反应基因^[11]、视黄酸代谢酶基因^[12]、细胞色素酶P450基因^[13]等, 在精神疾病的基因组学和精神药物基因组学方面取得了重要进展。除了探寻与疾病本身的关联作用, 研究遗传标记与某些定量疾病表型如精神分裂症阳性及阴性症状评分^[14]、攻击行为^[15]、脑室扩大^[16]及微小躯体异常^[17]等的关系也越来越受到重视。纵观这些病例对照关联研究, 也不乏阳性结果, 但样本例数相差较大 (病例组约200-700多例), 入组标准不一, 基因分型方法不同, 这可能也是关联研究难以彼此重复或验证的原因。有关候选基因多态性在精神分裂症家系中的传递不平衡检验仅有十多篇报道, 其中最新研究发现DNA甲基转移酶基因^[18]和*DAOA*基因^[19]在精神分裂症核心家系中存在传递不平衡, 而未见*KCNM3*^[20]和隐花色素-1^[21]基因多态存在传递不平衡现象。另一方面, 精神分裂症的全基因组扫描连锁研究主要集中在第1、6、13及22号染色体, 其中以唐氏等^[22]对湖南一个汉族精神分裂症多发家系进行与1q21-22、1q32-44、5q21-33、6p24-22、8p22-21、10p15-11、1q23-24、11p15、12q23-24、13q32-34、22q11-12、9q34、16p13、12q13、17q25和19q13等染色体区域64个微卫星位点的连锁分析最为全面。结果显示在11q23.2-24.2区域获得3个连续高的多点非参数分析LOD值, 并对11号染色体上的6个微卫星标记进行单体型分析, 显示D11s902和D11s898之间存在重组, 提示可能的疾病基因在D11s902远端。

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此外,随着人类基因组计划的完成及微阵列技术的迅猛发展,一种新的研究方法——全基因组关联研究已成为国际上新的研究热点。国外已有多篇关于精神分裂症^[23,24]、双相情感障碍^[25,26]、抑郁症^[27,28]、阿尔茨海默氏病^[29-31]等精神疾病的全基因组关联研究结果,但国内目前尚没有相关报道。仅有3篇报道分别运用基因芯片技术探寻精神分裂症患者外周血白细胞基因表达差异^[32]、抑郁症大鼠脑组织基因表达变化^[33]及筛选抗抑郁剂地昔帕明相关基因^[34]。所采用芯片包含的基因数分别为8464、5184和2048,样本例数为6至8例,未筛选显著差异表达的基因进行实时荧光定量聚合酶链锁反应检测加以验证。由此可见,我国精神疾病分子遗传研究虽然取得一定成果,但较国际水准仍存在一定的差距。

神经内分泌免疫学

自1977年Basedovsky和Sorkin^[35]最先提出神经内分泌免疫网路以来,大量研究证实精神疾病的发生与神经内分泌免疫系统调节紊乱有关。作为神经系统、内分泌系统和免疫系统三大系统之间资讯交流的重要物质,细胞因子是国内和国际精神疾病免疫研究的重点。如多篇研究报导首发精神分裂症和抑郁症患者血清细胞因子如白细胞介素(IL-2、IL-6、IL-8、IL-10、肿瘤坏死因子- α)水平较健康对照有显著性差异^[36-38],提示精神疾病的发生与细胞因子介导的免疫激活有关。宋氏等^[39]研究结果显示无论是基因转录或蛋白表达层面,精神分裂症均存在细胞因子水平异常。最新几项研究报导首发精神分裂症患者在接受氯氮平治疗6至8周后,细胞因子水平如IL-2、IL-6、IL-13及sIL-6R较治疗前有显著变化^[40-42]。是升高或降低,仍未有一致的结果。李氏等^[40]报导经氯氮平治疗6周后,IL-6、IL-13水平较治疗前显著升高,然而郭氏等^[43]报道经氯氮平治疗后4、8周及6个月的IL-6水平明显降低,并且8周末IL-6变化率与一般病理分减分率和总分减分率呈正相关。姚氏等^[44]报导选择性血清素回收抑制剂(SSRIs)抗抑郁药可明显降低抑郁症患者血浆IL-2和IL-6水平,并与5-羟吲哚乙酸升高呈负相关。尽管类似报导很多,多数研究的病例组样本量为25至30例,健康对照组为18至30例,观察时间为4至8周,主要采用酶联免疫或放射免疫法检测细胞因子水平。仅少数研究进一步探讨精神疾病免疫失衡的机制,如邱氏等^[45]发现糖皮质激素受体可能通过直接作用叉头样转录因数P3(Foxp3)或间接通过IL-10、转化生长因子- β 影响Foxp3及T调节细胞功能,继而出现Foxp3mRNA表达下降,CD4+CD25+T调节细胞数目减少、功能缺失,从而导致免疫失衡。

神经肽是另一类备受关注的神经激素、神经递质和神经调质。广泛参与机体多种生理功能如痛觉、睡眠、情绪、学习和记忆乃至神经系统分化和发育。目前发现与精神疾病有关的神经肽有P物质、神经肽Y、阿片肽、血管升压素、胆囊收缩素、神经降压素、内皮素等。国内研究较多的是抑郁症患者血浆^[46,47]或动物模型^[48,49]血浆、结肠组织及脑垂体中神经肽Y及P物质的表达水平,结果不甚一致,这与检测方法敏感性不同、采用不同的动物模型等因素有关。但对脑脊液采样研究较少,仅侯氏等^[50]采用酶联免疫吸附法测定

40例重性抑郁症患者、40例对照组脑脊液中P物质(SP)、神经肽Y、去甲肾上腺素、5-羟色胺及5-羟吲哚乙酸含量。结果显示患者组SP及NE含量均较对照组显著升高,复发性抑郁患者的NPY表达较首发明显高,提示重性抑郁症患者存在多种神经肽系统功能失调。同时,有少量研究报导神经肽水平变化可能有助于判断药物疗效。杨氏等^[51]对32例抑郁症患者应用帕罗西汀治疗6周后,血浆SP水平明显下降,其变化与HAM-D总分值的减分率呈显著正相关。陈氏等^[52]报导经氟西汀治疗8周后,抑郁症患者血浆SP含量明显降低,NPY明显升高,HAM-D及HAM-A评分均降低,提示神经肽可能是抗抑郁药物治疗的机制之一。

下丘脑垂体肾上腺轴功能亢进是抑郁症神经内分泌发病机制中被公认的机制之一。国内研究中值得关注的是某些中药成分对抑郁动物模型下丘脑垂体肾上腺轴功能及单胺类神经递质的影响。胡氏等^[53]采用慢性轻度不可预见性应激结合孤养大鼠抑郁症模型,发现胡椒碱具有良好抗抑郁作用,并可对抗慢性应激所引起的促肾上腺皮质激素释放激素及促肾上腺皮质激素升高。张氏等^[54]报导贯郁胶囊能纠正嗅球损毁抑郁症模型大鼠的行为改变,而1.2、0.6和0.3 g/kg的剂量能使血浆的促肾上腺皮质激素和皮质醇含量明显低于模型组。张氏^[55]参照Koizumi法改良,建立脑卒中后抑郁症大鼠模型;电镜观察发现舒肝健脑调郁片能明显减轻慢性应激对海马神经元的损伤,并且高剂量舒肝健脑调郁片和氟西汀均可降低模型大鼠下丘脑促肾上腺皮质激素释放激素mRNA表达,这可能是其抗抑郁机制之一。通过对中药作用机制的深入研究,植物性天然药物在精神疾病治疗中的比重也会逐渐加大。

电生理学

自1929年Berger首先应用常规脑电图以来,脑电生理学在精神医学中已逐渐得到广泛推广和应用。其中常规脑电图是目前最普遍、最实用的神经电生理技术,国内普及率已达95%。睡眠脑电图也逐渐成为研究精神疾病的重要研究手段。多篇研究分别观察了精神分裂症、抑郁症、强迫症、阿尔茨海默氏病等睡眠脑电图的变化特征^[56-60],其中欧氏等^[61]的比较分析显示抑郁症组在快速眼动睡眠的活动量、强度、睡眠时间、睡眠周期等均低于强迫症组和焦虑组,而后两者间差异无统计学意义。除自发脑电外,诱发脑电如视觉诱发电位、听觉诱发电位、事件相关电位包括关联性负变、P300、N400电位及失匹配性负波已成为脑电生理学研究的热点。作为事件相关电位最重要的内源性成分,P300是国际和国内研究最为深入的神经电生理指标。其中较为一致的发现是精神分裂症、抑郁症、老年性痴呆等患者的P300波幅降低,潜伏期延长^[62-64],经药物治疗后,抑郁症组P300波幅显著升高,潜伏期缩短^[65],而精神分裂症组无显著性差异^[66]。另一方面,有关P300到底是状态性标记还是遗传标记,至今尚无一致的看法。石氏等^[67]发现神经调节素1基因Arg38Gln多态与P300潜伏期有关联,而王氏等^[68]报导首发精神分裂症患者父母组P300波幅及潜伏期与正常对照组无显著差异,提示P300变化不存在家族聚集性,且P300电位变化与COMT基因多态

无关联。因此未能证实P300的这些变化是精神分裂症的遗传标记。当前脑诱发电位研究的另一个特点是将脑电生理学与其他研究方法如临床量表、心理测验、功能影像检查等相结合,综合考察疾病特性。国内与临床量表结合研究较多,如李氏等^[69]采用修改版外显攻击行为量表(MOAS)、冲动量表(BIS-11)和敌意量表(BDHI)的研究发现有攻击行为的男性患者比非攻击对照组事件相关电位P300潜伏期延长,振幅降低。刘氏等^[62]发现与阳性精神分裂症患者组比较,阴性组的听觉诱发电位潜伏期延迟,视觉诱发电位、听觉诱发电位和体感诱发电位波幅显著降低;同时,认知障碍因子仅与Fz、T3处P300波幅呈负相关,提示额及颞区P300波幅降低反映精神分裂症患者一定程度的认知损害。也有少量研究与心理测验、功能影像学结合如彭氏等^[70]应用P300电位与新推广的精神分裂症认知功能成套测验中文版(MCCB)相结合,发现P300的Fz、Cz、Pz点潜伏期、波幅分别与MCCB反映额叶、顶叶及枕叶相关测验结果相一致,从神经生理学和神经心理学两方面评定大脑认知功能。

精神药理学

在多种精神疾病的治疗方法中,药物治疗仍是主要的治疗手段。而精神药理学的研究为指导新药合成,推动精神病理生理化的理论研究提供了科学基础。目前,精神药理学研究主要集中在药物代谢动力学和药效学两方面。有多篇研究就精神活性药物如喹硫平、奥氮平、文拉法辛、帕罗西汀等的药代动力学^[71-74]进行了报道,而高效液相色谱法是目前常用的检测方法。也有研究试图探索药物代谢与代谢酶活性的关联^[75],血药浓度与临床疗效及副作用的关系^[76]等,这些研究结果对监测精神药物安全性及疗效提供个体化治疗方案都有一定的参考意义。精神药物遗传学的发展更从分子遗传的角度分析了精神活性药物疗效及副作用的个体差异,如多篇研究报道了CYP450基因^[77,78]、BDNF基因^[79]、5-羟色胺受体^[80]及多巴胺D2受体^[81]基因多态与药物疗效的关联,也有关于候选基因与药物副作用如迟发性运动障碍^[82-84]和体重增加^[85-87]的相关报导。虽然仍存在很多混杂因素如药物疗效的界定,过往抗精神病药物的使用等均可能影响结果的准确性和重复性,这些药物遗传学研究仍促进了基因导向性个体化用药成为事实。同时,寻找多个遗传标记及多个基因之间的相互作用,采用核心家系、同胞对等研究,并从缓解率或长时期预防复发来评价疗效等都是精神药物遗传学未来的发展趋势。

结论

综上所述,本文就我国生物精神病学的分子遗传学、神经内分泌免疫学、神经电生理学及精神药理学四方面研究进展作了回顾。从这些文献中,无论是动物模型还是临床患者,无论是采用分子遗传学、神经生化学、电生理学和药理学方法,都从不同角度对多种精神疾病的发病机理进行了广泛研究。虽然这些结果目前尚不能突破性地揭示精神疾病的生物学本质,但也为将来系统全面地认识疾病病理机制作出了贡献。

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