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胚胎期可卡因、吗啡暴露影响子代成瘾相关行为的神经发育机制*

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摘 要 孕期使用毒品可影响胎儿大脑的正常发育, 导致脑内神经递质系统异常以及行为的改变。近年来不断有研究证据提示, 胚胎期接触可卡因、吗啡等成瘾药物, 可以影响神经细胞的增殖、迁移或凋亡等发育过程, 使中脑皮层边缘系统中多巴胺、GABA、谷氨酸等神经元形态、受体功能以及突触可塑性发生改变, 从而导致子代的学习记忆和成瘾易感性等行为异常。本文将从行为、神经发育、递质系统以及脑功能等层面归纳胚胎期用药对成瘾相关行为影响机制的重要研究进展, 并试图提出可能的研究展望。

关键词 胚胎期; 可卡因; 吗啡; 脑发育; 成瘾行为
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孕期药物滥用严重危害子代身心健康,包括导致子代脑功能和成瘾易感性发生改变(Malanga & Kosofsky, 2003)。药物滥用的流行病学调查结果显示, 欧美等国家以滥用精神兴奋性剂可卡因为主, 而亚洲地区以滥用阿片类药物海洛因为主, 人群以 35 岁以下的育龄人口为主(Jansson, Velez, & Harrow, 2009)。这两类药物都能够透过胎盘屏障和胎儿的血脑屏障, 对子代脑发育和行为产生严重影响(Thompson, Levitt, & Stanwood, 2009)。可卡因主要通过结合脑内多巴胺能神经元的突触末梢处的单胺类转运体, 并抑制多巴胺(dopamine, DA)的转运和重吸收, 导致突触间隙 DA 聚集, 从而改变受体后正常的细胞信号转导活动(Badiani et al., 2011); 而海洛因或吗啡则首先与 GABA 能神经元上的阿片类受体结合, 导致 GABA 能神经元活动增强, 扰乱受体后的细胞信号转导机制(Badiani et al., 2011)。近年来, 许多来自动物实验的研究证据表明, 胚胎期成瘾药物暴露会改变子代神经系统的正常发育过程, 导致脑内重要的神经递质系统的神经元形态和功能异常以及子代行为的改变(Slamberová, 2012)。本文比较了胚胎期可卡因暴露(prenatal cocaine exposure, PCE)或者胚胎期吗啡暴露(prenatal morphine exposure, PME)对细胞增殖、迁移、凋亡等发育过程的影响, 对中脑皮层边缘系统(mesocorticolimbic system, MCLS)的神经递质系统影响的研究证据, 以期深入理解胚胎期药物暴露导致子代成瘾易感性改变的神经发育机制。

1 胚胎期接触成瘾物质对子代影响的行为表现

1.1 对成瘾行为的影响

胚胎期使用成瘾药物会改变子代的奖赏特性和动机行为, 反映了其成瘾易感性的变化。目前, 判断易感性改变的行为范式主要包括静脉自身给药(intravenous self-administration, IVSA)、颅内自我刺激(intracranial self-stimulation, ICSS)、条件性位置偏爱(conditioned place preference, CPP)、精神运动和敏化(locomotor stimulation and sensitization,

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LS)。有一系列研究证据表明, 胚胎中后期可卡因暴露增加可卡因诱导的 IVSA (Keller et al., 1996b; Keller & Snyder-Keller, 2000; Rocha, Mead, & Kosofsky, 2002)、ICSS (Malanga et al., 2008) ; 也有相反的证据提示, 胚胎中后期可卡因暴露降低或不影响可卡因诱导的 CPP (Heyser et al., 1992b; Malanga, Pejchal, & Kosofsky, 2007; Murphy et al., 1999)、降低或不影响可卡因诱导的 LS (Crozatier et al., 2003; Guerriero et al., 2005; Lu, Lim, & Poo, 2009)、增加可卡因诱导的刻板行为(Crozatier et al., 2003; Guerriero et al., 2005)。

胚胎期海洛因或吗啡暴露对子代易感性改变的直接证据仍然较少。但是, 有不少来自临床的证据提示, 孕期使用吗啡可导致胎儿发育畸形、认知功能低下、痛觉敏感性下降(Bandstra et al., 2010)。近年来, 一些来自啮齿类和鸟类动物的结果表明, PME 不影响吗啡诱导的 IVSA (Riley & Vathy, 2006), 增加或者不影响吗啡诱导的 CPP 和 LS (Riley & Vathy, 2006; Wu et al., 2009); 通过在胚胎发育的不同阶段进行成瘾药物暴露, 发现胚胎晚期接触吗啡会增强日龄小鸡吗啡诱导的 CPP, 而胚胎早期吗啡暴露弱化吗啡诱导的 CPP, 降低学习记忆能力(He et al., 2010; Jiang et al., 2011)。

1.2 对学习记忆的影响

成瘾与学习记忆有密切关系, 药物成瘾被认为是一种异常的学习过程(Torregrossa, Corlett, & Taylor, 2011)。学习记忆的功能改变可能会影响成瘾相关行为。许多研究表明, 不论是 PCE 还是 PME 均损害子代的学习记忆功能(Nasiraei-Moghadam et al., 2012; Riggins et al., 2012)。以 Morris 水迷宫为范式的研究发现, PCE 或者 PME 增加寻找站台任务的潜伏期, 在训练区域的停留时间缩短, 提示胚胎期成瘾药物暴露损害了子代的空间学习记忆能力(Meunier & Maurice, 2004; Niu et al., 2009; Trksak et al., 2007)。另外, 使用八壁迷宫为范式的研究发现, PCE 或者 PME 可弱化子代的工作记忆能力 (Meunier & Maurice, 2004; Schindler, Slamberova, & Vathy, 2001)。

成瘾行为的一个重要特点是, 成瘾者对于成瘾药物相关的环境、线索存在异常持久的记忆。基于经典条件反射原理, 用药环境和成瘾药物欣快感之间的联想性学习(associative learning, AL)在成瘾记忆的形成中起重要作用。胚胎期成瘾药物暴露对 AL 影响的研究表明, PCE 降低了子代的 AL 能力(Heyser et al., 1992a; Meunier & Maurice, 2004)。我们的结果也提示, PME 导致小鸡的一次性被动回避学习行为弱化, 参与学习记忆的主要核团之一中间腹内侧原皮质(intermediate medial mesopallium, IMM) 的长时程增强(long-term potential, LTP)和双脉冲比值(paired-pulse ratio, PPR)显著降低(Jiang et al., 2011)。

2 胚胎期成瘾药物暴露影响脑发育过程

DA 是脑发育中最早出现的神经递质之一(Puelles & Verney, 1998)。小鼠的络氨酸羟化酶正性标记的细胞在胚胎第 11 天出现在腹侧中脑, 多巴胺能神经轴突进入新纹状体在胚胎第 12~13 天, 进入大脑皮层会再晚 2 天(Ohtani et al., 2003; Popolo, McCarthy, & Bhide, 2004)。小鼠的 μ 阿片受体出现在胚胎期发育第 12.5 天, κ 受体出现在第 14.5 天, μ 和 κ 受体的表达从 E14.5 到 E18.5 天迅速增加(Rius et al., 1991)。可卡因和吗啡分别作用于多巴胺能系统和阿片受体, 会干扰受体后信号, 影响正常的脑发育。胚胎期成瘾药物暴露对脑发育过程的影响包括影响神经细胞的增殖、迁移、凋亡等发育过程。

2.1 细胞增殖

神经前体细胞(neural progenitor)的增殖是决定神经元数量和大脑细胞构筑的重要因素。研究发现, PCE 可诱导新皮层细胞构筑异常包括导致皮层神经元数量的降低以及皮层神经元定位的异常。这些反应只出现在胚胎发育中期可卡因暴露的个体, 而这个阶段是神经前体细胞增殖最活跃的阶段(Lidow, Bozian, & Song, 2001)。PCE 会抑制细胞增殖, 其分子机制与 PCE 下调细胞周期蛋白 A (cyclin A)有关(Lee et al., 2008)。细胞周期蛋白 A 的作用是使分裂中的细胞从有丝分裂的 G_1 期转换到 DNA 复制的 S 期。研究发现, 通过基因导入手段增加细胞周期蛋白 A 会翻转 PCE 导致的增殖抑制作用(Lee et al., 2008)。直接考察 PME 与细胞增殖的研究较少。使用斑马鱼的研究发现吗啡可通过激活阿片受体, 增加 Wnt1(编码调控神经增殖、分化的信号蛋白)的表达, 促进细胞增殖(Sanchez-Simon et al., 2012)。

2.2 细胞迁移

PCE 影响神经元放射性迁移的直接证据未见

报道。有研究表明, PCE 改变神经胶质细胞的放射性迁移(Gressens, Kosofsky, & Evrard, 1992), 由于神经元的迁移需要胶质细胞的引导, 推测 PCE 也会影响皮层神经元的放射性迁移。来自灵长类动物的研究表明, PCE 导致皮层神经元出现在皮层的Ⅳ,Ⅴ,Ⅵ层和白质区域, 而不是限于皮层的第Ⅳ,Ⅴ层(Lidow et al., 2001), 神经元定位的改变提示放射性迁移过程的可能受损。对神经元切线迁移的研究结果发现, PCE 阻碍了神经元从基底前脑的神经节隆起(ganglionic eminence, GE)到背侧大脑皮层的迁移。由于从 GE 迁移到皮层的神经元主要是 GABA 能, 研究进一步检查大脑皮层 GABA 能神经元数量发现, PCE 大鼠的皮层 GABA 能神经元数量减半, 提示 PCE 阻碍了 GABA 能神经元到皮层的迁移(Crandall et al., 2004)。细胞培养的研究显示, 吗啡增加神经胶质细胞的迁移(Horvath & DeLeo, 2009)。

2.3 细胞凋亡

胚胎期成瘾药物暴露增加细胞凋亡。细胞凋亡是脑发育过程的重要环节, 在发育中必然出现。中枢神经系统约有至少 50%~80%的神经元细胞发生凋亡, 胚胎期及出生后的发育期多次出现的凋亡高峰与清除过多的细胞及神经联系有关, 从而使细胞数量得以调整,建立起精确的神经回路(Vogel, 1993)。PCE 可增加促进细胞凋亡的蛋白 Bax 的表达, 也增加抑制细胞凋亡蛋白 Bcl-2 的表达, 升高 Bax/Bcl-2 的比例, 并增加调控凋亡的另外一个重要蛋白 caspase-3 的表达(Xiao & Zhang, 2008)。PME 也升高 Bax、caspase-3、Bax/Bcl-2 的表达, 但会降低 Bcl-2 的表达(Nasiraei-Moghadam et al., 2010)。

3 胚胎期成瘾药物暴露影响皮层的细胞构筑

胚胎期成瘾药物暴露对神经细胞的正常发育(增殖、迁移、凋亡)过程的影响可导致子代脑内的细胞构筑异常。研究发现, 大脑皮层是受胚胎期药物作用影响较大的脑结构(W. Wang et al., 2012)。胚胎期成瘾药物暴露可改变皮层神经元的细胞构筑, 包括改变神经元形态、神经元数量、受体表达水平等。

3.1 神经元形态

PCE 或 PME 改变神经元形态。树突棘是突触输入的重要靶点, 其形态或数量的改变会使神经环路功能异常。PCE 增加前额叶皮层(prefrontal cortex, PFC)或躯体感觉皮层或扣带皮层的椎体神经元的树突分支数和树突长度、棘密度(Lu et al., 2012; Stanwood et al., 2001; Xiao & Zhang, 2008); 而 PME 降低视皮层的第 2、3 层的椎体神经元的树突长度、分支数量和棘密度(Mei et al., 2009), PME 对 PFC 或躯体感觉皮层神经元形态的影响未见报道。有研究显示胚胎期海洛因暴露会减少躯体感觉皮层的椎体神经元的树突分支和树突长度(Lu et al., 2012)。

3.2 神经元数量

皮层的椎体神经元会分泌谷氨酸, 支配皮层下脑结构。GABA 能神经元作为局部环路神经元, 通过 GABA 受体起到调控椎体神经元兴奋性的作用(Connors & Gutnick, 1990)。胚胎期成瘾药物对椎体神经元、GABA 能神经元数量的影响会破坏兴奋性神经元和抑制性神经元之间的平衡, 使皮层功能受损。PCE 增加额叶, 而并非内侧前额叶(medial prefrontal cortex, mPFC)的椎体神经元数量 (McCarthy & Bhide, 2012)。对 GABA 能神经元的影响发现, PCE 降低 mPFC, 而并非额叶的 GABA 能神经元数量, 特别是降低表达钙调节蛋白的 GABA 能神经元数量 (Buxhoeveden et al., 2006; McCarthy & Bhide, 2012)。PME 对皮层神经元数量的影响未见报道, Walhovd KB 等使用脑成像的研究显示胚胎期海洛因暴露的儿童大脑皮层容量降低(Nasiraei-Moghadam et al., 2010), 并且 PME 可降低海马齿状回的 GABA 能神经元的数量(Niu et al., 2009)。

3.3 受体表达

PCE 对 GABA 受体的影响具有脑区特异性。在 PFC, PCE 降低 $GABA_A$ 受体的 alpha1、gamma2 和 delta2 亚基(Huang, Liang, & Hsu, 2011); 在扣带皮层, PCE 增加 $GABA_A$ 受体的 alpha1 亚基, 降低 beta2 亚基, 不影响 gamma2 亚基(Shumsky et al., 2002); 在视皮层, PCE 不影响 $GABA_A$ 受体的表达(Shumsky et al., 1998)。未见 PME 对皮层 GABA 受体影响的报道, 但在海马, PME 上调 CA1 区的 $GABA_A$ 受体的 alpha1 亚基, 下调 beta2 亚基(Wang et al., 2011)。胚胎期成瘾药物暴露对谷氨酸受体影响的研究发现, PCE 不影响 mPFC 谷氨酸受体的 GluR1 亚基(Lu et al., 2009), 虽未见有关 PME

对于皮层谷氨酸受体影响的报道，但 NMDA 受体拮抗剂能够弱化 PME 引起的新生儿的戒断症状(Yeh et al., 2002)。

4 胚胎期成瘾药物暴露影响 MCLS 功能

由于成瘾药物作用于 MCLS 发挥强化效应，所以胚胎期成瘾药物暴露对 MCLS 功能的影响是子代成瘾易感性改变的重要神经基础。MCLS 起源于腹侧被盖区(ventral tegmental area, VTA)，并主要投射至伏隔核(nucleus accumbens, NAc)和 PFC。尽管不同成瘾药物发挥作用的靶分子不同，但是最终都会增加 VTA 投射区域的 DA 浓度(Nestler, 2005)。胚胎期成瘾药物暴露可弱化多巴胺能神经元功能、多巴胺受体功能，改变皮层突触可塑性。

4.1 多巴胺能神经元功能弱化

PCE 可降低 VTA 的 DA 神经元的基础放电率，但是不影响 DA 受体激动剂阿扑吗啡诱导的 DA 神经元的放电率，提示 PCE 可改变突触前 DA 神经元的活动(Minabe et al., 1992)。突触后 DA 释放的研究结果显示，PCE 增加 NAc (腹侧纹状的重要组成)处基础状态下的 DA 释放，以及可卡因诱导的 DA 释放(Keller et al., 1996a; Malanga,et al., 2009)。但在背侧纹状体，PCE 导致基础状态下 DA 的水平降低，电刺激诱发的 DA 释放也减少，突触前的 DA 重摄取增多(Glatt et al., 2004)。和可卡因不同，PME 不影响纹状体的 DA 释放(Vathy et al., 1994)。

4.2 多巴胺 D1 受体功能弱化

已有研究结果显示，PCE 会弱化 D1 样受体与 G 蛋白的偶联状态，其机制可能是调节了蛋白激酶和磷酸激酶之间的平衡(Unterwald et al., 2003; Wang, Yeung, & Friedman, 1995)。可卡因本身能够抑制蛋白磷酸酶 1，此作用会导致 D1 受体与 G 蛋白不偶联，从而降低 D1 受体功能(Zhen et al., 2001)。然而，PCE 作用对于 D1 受体的结合点密度、蛋白表达或者受体 mRNA 的表达，由于药物剂量、可卡因作用时间、动物种类等因素结果并不太一致(Friedman, Yadin, & Wang, 1996; Kubrusly & Bhide, 2010; Tropea et al., 2008)。PCE 对 D2 受体的影响并不很清楚。有研究显示，PCE 引起大脑皮层和基底前脑 D2 受体的功能活性增加(Ferris et al., 2007)。和可卡因作用的相反，离体脑片的结果显示，PME 通过突触后的 DA1 受体会增强纹状体的 DA 传递(Schoffelmeer et al., 1997)。

4.3 皮层突触可塑性改变

来自兔子或小鼠的实验均发现 PCE 可易化 mPFC 椎体神经元 LTP 的产生，使得 mPFC 的椎体神经元的兴奋性增强(Huang et al., 2011; Lu et al., 2009)。虽未直接看到 PME 对皮层可塑性影响的报道，但 PME 可降低参与调节突触可塑性作用的蛋白水平，比如 BDNF 或 Ca^{2+} (Nasiraei-Moghadam et al., 2012)，并且 PME 会弱化大鼠的海马齿状回的突触可塑性(Niu et al., 2009)。我们的研究结果也显示，PME 弱化了小鸡的 IMM (相当于哺乳动物的联合皮层)的 PPR 和异突触的 LTP (Jiang et al., 2011)。

5 研究展望

孕期吸毒对子代的主要影响是使胎儿脑发育过程发生变化，进而导致子代行为异常。研究胚胎期接触成瘾物质对于胎儿脑发育和行为的影响及其机制有重要的理论和现实意义。有几点展望值得期待：1)育龄人口药物滥用对子代有严重危害，使用动物模型模拟胚胎期药物滥用对子代影响具有重要的现实意义。子代的脑发育不仅受成瘾药物影响，还受到营养、环境应激或情绪等母体状态的影响。因此，用啮齿类甚至灵长类动物研究胚胎期成瘾药物暴露对子代行为的影响，很难避免一些间接因素的作用。鸟类虽在进化上低于哺乳动物，但鸡胚发育可以在人工控制的孵化条件下进行，可考察成瘾药物的单独作用，排除母体影响。小鸡出生后神经系统发育早熟、无需亲代照顾、出生后第一天就能独立活动，这些特点使得用小鸡作为模式动物能够较好地避免出生前后外界环境的影响因素。2)胚胎期成瘾药物暴露直接影响了脑发育过程，胚胎期成瘾药物暴露如何调控细胞的增殖、迁移、分化、凋亡等发育过程需要进一步研究。3)胚胎发育是个动态的过程，目前光学成像技术和遗传学标记技术的发展，使得在不同的发育阶段在体观察目标基因、神经元、蛋白的变化状态成为可能，利用这些技术可极大推进胚胎期成瘾药物影响子代脑发育机制的研究。(4)使用细胞替代治疗恢复胚胎期成瘾药物暴露导致子代的行为或脑功能异常。神经前体细胞移植是细胞替代治疗的重要方法(Bjorklund &

Lindvall, 2000)。移植的神经前体细胞会迁移到受损脑区, 替代受损细胞, 恢复脑区功能。目前, 已有研究在海马通过移植神经前体细胞翻转由脑损伤或老龄化引起的认知缺陷(Qu et al., 2001; Shear et al., 2004), 亦有通过移植胚胎干细胞翻转胚胎期海洛因暴露引起的胎儿畸形(Kazma et al., 2010)。人类中, 胚胎期成瘾暴露更多地表现为脑功能的异常, 深入研究细胞治疗对脑功能的恢复作用有重要的现实意义。

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Neurodevelopmental Mechanisms of Prenatal Cocaine or Morphine Exposure on Addiction-related Behaviors in Offsprings

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Abstract: Prenatal exposure to addictive drugs can influence the development of fetal brain, leading to abnormality of the main neurotransmitter system and behavioral malfunction. Recent studies showed that prenatal exposure to cocaine or morphine affects the proliferation, migration and apoptosis of neural progenitor, resulting in changes of neuronal morphology, receptor function and synaptic plasticity. Such changes are widely found in dopamine, GABA and glutamate system in mesocorticolimbic system, which leads to behavioral deficits in learning and memory and altered susceptibility to addictive drugs. Here we summarize related studies on behaviors, neural development, neurotransmitter system and brain function and try to put forward further research prospects.

Key words: embryonic period; cocaine; morphine; brain development; addiction behavior