

孕期应激对绵羊子代表型编程效应研究进展

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摘要 家畜孕期应激对子代行为、生理和神经方面有着复杂的影响,这种影响可以持续到子代成年甚至跨代遗传。家畜孕期管理不当会对母体产生应激,使母体及其子代的生长、健康和福利受损,从而影响家畜的经济价值。本文以绵羊孕期应激模型和人工合成糖皮质激素模拟应激模型的试验结果为切入点,系统总结了绵羊孕期应激对子代表型的影响,并讨论了研究结果异同的可能原因。研究发现,绵羊孕期应激可以影响子代出生体重、调节子代下丘脑—垂体—肾上腺轴发育、影响子代行为模式和认知能力、改变子代基因表达和大脑形态,并且母体糖皮质激素水平是决定子代表型变化的主要因素。未来研究方向应该侧重于绵羊孕期应激对子代基因表达、免疫功能、生产性能和母性行为的影响,以及不同妊娠时期母体应激的比较研究、对子代影响的连续研究和探讨孕期应激不良编程的应对策略研究。

关键词 绵羊; 编程效应; 孕期应激; 表型

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Research progress on the programming effects of prenatal stress in sheep on its offspring's phenotype

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Abstract Prenatal stress results in complex behavioral, physiological and neurological consequences for the developing of offspring, which can last into adulthood or even propagate to subsequent generations. Inadequate management practices of the farm animals during pregnancy may be potential stressors for the mother, with detrimental effects on the growth, health and welfare of the dam and its offspring, and thus can affect the economic consequences of the farm animals. The outcomes from different experimental models using either maternal stress paradigms or artificially increased maternal glucocorticoid are presented, the effects of prenatal stress on the phenotype of the offspring are systematically summarized, and possible reasons for consistent or divergent results are discussed. It is revealed that the prenatal stress can impair birth weights, regulate the development of hypothalamic-pituitary-adrenal axis, modify behaviour pattern and cognitive ability, and alter gene expression and brain morphology of the offspring. There is evidence that the maternal glucocorticoid regulation is a major determinant of the alterations in offspring. Further research should focus on the gene expression, immune function and production performance in offspring and maternal behavior in female offspring used as breeding animals, as well as the comparative study of prenatal stress during

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different gestational period, the continuous study of the effects of prenatal stress on the offspring and the treatment strategies that effectively reverse the detrimental programming effects of prenatal stress.

Keywords sheep; programming effects; prenatal stress; phenotypes

动物成年后的表型是遗传和母体孕期环境共同作用的结果^[1]。人类和啮齿动物的研究表明母体孕期经历的环境对子代的行为和生理系统有编程效应,特别是在母体营养不良、感染传染病或者经历应激事件等情况下,编程效应尤其明显^[2-3]。孕期应激可以影响子代行为^[4]、生长发育^[5-6]、繁殖和生产力^[6]、大脑^[7]、神经内分泌^[8]、免疫体系^[9]和基因表达^[10]等。除此之外,孕期应激还可以通过影响母性行为,改变母体对子代的抚育质量,从而对子代大脑和行为发育产生不利影响,已有研究表明孕期应激对母性行为的影响可能会通过非遗传机制传递给子代^[11]。

孕期应激对子代的“编程”通过内分泌调节发挥作用,孕期应激导致子代下丘脑-垂体-肾上腺轴(Hypothalamic-Pituitary-Adrenal Axis, HPA 轴)的应激变化,甚至可以引起子代 HPA 轴功能的永久性改变^[12],对子代的行为和生理等方面产生终身影响,增加子代患精神疾病、心血管疾病和代谢性疾病的风险^[13-14]。绵羊孕期可能暴露在各种应激环境中,例如:剪毛、运输、噪音、畜舍环境、更换饲料、社群应激等。绵羊孕期应激造成母体代谢紊乱,损害母子健康和福利,影响家畜的经济价值。近年来对绵羊孕期应激的研究较多,本文拟对绵羊孕期应激对子代生长、行为、内分泌、大脑神经元结构、基因表达、心血管功能和健康的影响的相关研究进行综述,探讨孕期应激不良编程的应对策略,以期给孕期应激对绵羊子代编程效应的进一步研究提供依据。

1 编程效应

哺乳动物胎儿发育不仅受母体激素和内分泌作用的直接影响,也受胎盘功能和营养供给改变的间接影响^[15]。在妊娠期,胎盘糖皮质激素屏障—胎盘酶 11 β -羟基类固醇脱氢酶 2(11 β -HSD2)能够将具有生物活性的糖皮质激素皮质醇脱氢氧化为无生物活性的 17-羟-11-脱氢皮质酮,使母体与胎儿之间糖皮质激素浓度差保持在约为 10:1 的梯度,从而保护胎儿免受母体高浓度糖皮质激素的伤害。然而,人类和动物模型研究表明,孕期应激可以增加母体皮质醇水平,降低 11 β -HSD2 的酶活性,使经胎盘转

移给胎儿的具有生物活性的皮质醇水平升高^[16-17]。糖皮质激素通过结合糖皮质激素受体和盐皮质激素受体来影响发育中的胎儿,并作为转录因子改变基因表达;同时,糖皮质激素在神经系统,特别是在海马区,可以通过膜糖皮质激素受体介导的非基因作用方式对神经生理和行为产生影响^[18-19]。因此,在哺乳动物中,糖皮质激素成为将母体应激传递给胎儿的主要介导者,能够穿越胎盘屏障来影响胎儿组织的成熟和分化^[17]。应激情况下,母体其他内分泌环境的变化也可以影响胎盘功能,例如,儿茶酚胺能够降低子宫血流量^[20]、抑制胎盘 11 β -HSD2 mRNA 的表达^[21]。而且,母体内分泌环境的变化可能会通过表观遗传机制来编程出生后的表型,例如,改变胎盘 11 β -HSD2 DNA^[21]和糖皮质激素受体基因的甲基化水平^[22]。

“编程”这一概念诠释了生物体经历的环境事件和稳定的表型改变之间的关联,编程效应则反映 1 个特定因素在发育期对靶组织的组织模式和基因表达模式的影响,进而影响靶目标在生物体整个生命周期中的功能^[23]。哺乳动物在编程过程中,母体所经历的环境应激传递给胎儿,并在发育敏感时期作用于特定组织,改变胎儿发育轨迹、组织和功能。目前解释胎儿编程的作用机制有 2 种,分别为胎儿营养不良假说和胎儿糖皮质激素过量暴露假说^[23-24]。这 2 种假说并不互相排斥,因为应激可能会减少母体的食物摄入量,从而引起母体和胎儿的应激反应^[25]。此外,母体糖皮质激素可能介导了饮食对胎儿生理学特性的影响。已有研究表明孕期大鼠低蛋白饮食导致断奶后子代血压升高,但阻断母体糖皮质激素合成可以消除蛋白质限制对子代的影响^[25-27]。也有研究采用“发育编程”这一概念解释孕期应激、胎儿生长发育的改变与成年后疾病之间的关系^[28]。

2 绵羊孕期应激对子代的影响

孕期应激可以使母体产生消极、痛苦的情绪,严重影响母体内分泌平衡,进而导致子代正常发育的激素环境发生变化,改变子代 HPA 轴功能和皮质醇分泌能力,可能对子代的行为、健康、生产力和适

合度产生重要影响。研究表明,母猪孕期暴露于社群、物理或环境应激影响子代的生长发育、行为模式、免疫系统和神经内分泌功能^[29];肉牛和奶牛孕期应激影响子代的福利和生产性能^[30];人类孕期应激对胎儿HPA轴功能的编程效应被认为是子代精神疾病和心血管疾病的重要病因之一^[31]。

2.1 对子代生长的影响

绵羊孕期应激对子代生长影响的研究主要是对体重及存活率影响方面,尤其以孕期剪毛应激的研究最为集中,但是已有的研究结果却不尽相同。一些研究结果表明孕期剪毛不影响子代的出生体重^[32],而大多数研究结果表明孕期剪毛可以增加子代的出生体重、存活率和断奶时体重^[33-34]。孕期剪毛对单胎或者双胎子代体重影响的研究结果也不一致:Corner等^[35]发现孕中期剪毛可以增加双胎和单胎出生体重;Jenkinson等^[36]发现孕中期剪毛可以增加双胎的出生体重,但是对单胎的出生体重无影响。

绵羊孕期剪毛对子代出生体重的影响之所以会出现研究结果不一致的情况,可能是由于影响子代生长的环境因素比较复杂。剪毛虽是1种短期强应激,但从长远看,有利于母羊驱虫、身体舒适、增加采食等,这种长期效应会给绵羊胎儿带来正面影响。另外,剪毛时所处季节环境条件的不同、母羊对应激反应的不同等均可以影响绵羊子代的生长发育。绵羊在妊娠100d左右,胎盘重量增加到峰值,Morris和McCutcheon^[37]研究发现孕中期剪毛会影响母羊胎盘发育,对子代出生体重的影响要比孕晚期大,因此,绵羊孕中期剪毛所引起的子代体重增加是提高子代存活率的主要原因之一^[32]。Barbieri等^[38]比较了不同妊娠时期绵羊剪毛对子代的影响,结果表明孕中期剪毛子代的出生体重显著高于孕晚期剪毛子代,但是剪毛时期对子代72h存活率和断奶时体重无影响。综上,虽然绵羊孕期剪毛对子代出生体重影响的研究结果存在不一致,但公认孕期剪毛在很大程度上会增加子代的出生体重^[32]。

绵羊孕期其它应激事件对子代出生体重也有影响。Roussel等^[39]对分娩前5周的绵羊进行隔离应激(2次/周,1h/次),发现子代出生体重显著增加,并且增加趋势一直持续到断奶时。Roussel等^[40]进一步研究发现,当1组母羊暴露于相似的隔离应激条件(ISOL组),另外1组母羊暴露于隔离应激和运输应激同时存在的条件(TRAN组)时,2组母羊

的子代出生体重没有变化,但是断奶时ISOL组体重显著高于TRAN组和对照组。Hild等^[41]在孕晚期分别利用厌恶(Aversive)和温和(Gentle)事件对绵羊进行应激处理,发现不同处理间子代出生体重的差异不显著,仅是母羊暴露于厌恶事件的子代刚出生时和1周龄时体重较重。Early等^[42]在孕中晚期(妊娠64d~分娩前)对绵羊进行慢性热应激,在妊娠136~141d测量,发现无论是胎儿体重还是胎盘重量均显著低于对照。McCrabba等^[43]在孕早中期(妊娠30~80d)对绵羊进行慢性热应激,发现无论是热应激结束时(妊娠80d)还是在妊娠140d,胎盘重量均显著降低,然而胎儿重量和尺寸在热应激结束时(妊娠80d)与对照相比无显著差异,但是在妊娠140d时则显著降低。因此,绵羊不同妊娠时期的慢性热应激均可以显著降低胎儿出生体重,这可能是由于母体慢性热应激可以限制胎盘生长^[44]和细胞生长^[42,44],减少子宫血流量^[45],降低母体采食量、孕酮和羊胎盘催乳素分泌^[46],从而影响胎儿生长。

绵羊胎儿对母体孕期人工合成糖皮质激素应激处理很敏感,对其生长和内分泌的影响可能持续到出生后。母体孕晚期(妊娠104、111和118d)反复倍他米松(0.5mg/kg)处理不仅可以降低妊娠125和146d绵羊胎儿体重^[47],还可以降低羔羊出生体重、6周龄前体重和3月龄体重^[48-49],并且子代胎儿血浆胰岛素、瘦素和三碘甲状腺原氨酸的表达量在胎儿出生前后的不同发育时期也有所下降^[49]。母体孕早期(妊娠40~42d)注射地塞米松(0.14mg/kg,每隔12h注射1次,共注射4次),对50、101、140d子代胎儿体重和器官重量的影响各不相同,没有一致性结果,但可以降低7月龄雌性子代的垂体、肾上腺、肝脏和肾脏的重量^[49]。综上,绵羊胎儿生长受母体糖皮质激素处理的影响,并且因激素处理时间和测量时子代年龄段的不同而呈现出不同的影响效果。

2.2 对子代神经内分泌功能和行为的影响

HPA轴是神经内分泌系统的重要部分,参与控制应激反应,并调节许多生理活动。在HPA轴中,下丘脑分泌的促肾上腺皮质激素释放激素和加压素刺激垂体前叶释放促肾上腺皮质激素(Adrenocorticotrophic Hormone, ACTH),ACTH又刺激肾上腺皮质合成和释放糖皮质激素,同时,糖皮质激素还可以负反馈调节HPA轴。孕期应激会

使母体血液及胎盘内糖皮质激素水平升高,改变胎儿正常发育的激素环境。大鼠孕期应激引起胎儿糖皮质激素受体和盐皮质激素受体表达量下调,并影响子代幼年期和成年期 HPA 轴的反馈调节^[50]。因此,Meaney 等^[23]认为 HPA 轴不仅是环境应激所影响的靶目标,而且是个体早期生活事件与成年期健康之间关系的调节者。绵羊孕期应激对子代 HPA 轴发育影响的研究有限,且由于受应激事件、应激时期和测试时子代年龄的影响,研究结果也不尽相同。绵羊孕晚期(分娩前 5 周)隔离应激(2 次/周,1 h/次)可以增加 25 日龄子代的血液皮质醇浓度,但对 1、3、8 月龄子代的血液皮质醇浓度无影响^[39-40]。Florian 等^[51]比较了母体内源性皮质醇和人工合成糖皮质激素应激对胎儿 HPA 轴发育的影响,他们在孕早期(妊娠 30~100 d)和孕晚期(妊娠(100~120 d)±2 d)对绵羊实施隔离应激(每周 2 次,3 h/次)或者在孕晚期(妊娠 106、107、112 和 113 d)对绵羊服用倍他米松($2 \times 110 \mu\text{g}/\text{kg}$),然后在 HPA 轴成熟前(妊娠 112 d)和成熟期间(妊娠 129 d),测量了胎儿皮质醇对低血压挑战的响应,结果发现无论是孕早期和孕晚期的隔离应激还是孕晚期服用倍他米松均不能改变 112 d 胎儿的皮质醇响应,但是均增加了 129 d 胎儿的皮质醇响应,这表明暴露于母体物理应激和人工合成糖皮质激素均可以改变胎儿 HPA 轴功能的设定点,并以类似的方式增加了孕晚期 HPA 轴的活性。因此,绵羊胎儿 HPA 轴发育在整个妊娠期均易受母体糖皮质激素水平的影响,而且在孕早期最易受影响。但是,也有研究表明孕中期剪毛应激对绵羊 39 日龄子代 HPA 轴的发育无影响^[35]。

Thorsten 等^[52]在孕早期(妊娠 40~41 d)对母羊注射地塞米松(每 12 h 0.14 mg/kg),研究发现胎儿 HPA 轴的发育轨迹发生了改变,肾上腺活性增强。Sloboda 等^[47,53-54]在孕晚期对绵羊反复注射倍他米松(妊娠 104 d 开始,1 次/周,注射剂量为 0.5 mg/kg),发现可以显著增加妊娠 125 d 子代胎儿皮质类固醇结合能力和妊娠 146 d 子代胎儿的血浆 ACTH 水平;影响 6 月龄~1 岁之间子代 HPA 轴功能,增加子代肾上腺敏感性;增加 2 岁子代垂体活力,降低 2 岁和 3 岁子代肾上腺 ACTH 敏感性。以上研究表明:孕期人工糖皮质激素对绵羊子代 HPA 轴的编程效应受子代年龄差异的影响,可以长期引起子代 HPA 轴的活性和功能的变化;肾上腺

活性在子代早期表现出敏感性增强,到子代 2 岁时肾上腺敏感性开始降低,并且这种降低持续到 3 岁。总之,绵羊胎儿 HPA 轴发育易受孕期应激和人工糖皮质激素应激的影响,并且孕期不同时期应激可能对子代 HPA 轴的影响效果不同,不同龄子代对母体孕期应激的响应也不同。

当母体暴露于应激环境时,所产生的过量糖皮质激素能够影响胎儿大脑的神经联系,以及神经递质的活性和可塑性,损害子代的认知能力^[55]。绵羊孕期应激对子代行为编程效应受应激事件的种类、强度和持续时间的影响,并且对不同月龄子代行为的影响各不相同。Coulon 等^[56]在绵羊孕晚期(分娩前 5 周)利用厌恶性的人类自身活动事件对母体进行慢性应激处理,子代 25~34 d 时进行人接近、惊吓和迷宫试验,发现子代消极恐惧反应增加,空间学习和工作记忆能力不受影响。之后,Coulon 等^[57]在该项研究的基础上,增加了应激原的种类和强度,在绵羊孕晚期(妊娠 94~143 d)利用多种厌恶事件对母体进行慢性应激处理,在子代 1~3 月龄时对其进行行为测验,发现子代情绪反应和恐惧反应增加,认知判断能力下降,出现了消极判断和学习缺陷,空间学习和工作记忆能力下降。Coulon 等^[56-57]在这两项研究中,试验结果出现不同情况,可能是因为厌恶应激的应激原和应激时间长短不同而引起的:Coulon 等在 2011 年的研究中,应激原主要是与人类自身活动相关,种类只有 5 种,应激时间为 5 周;而在 2015 年的研究中,应激原涉及到人类生产管理的很多方面,种类增加到了 15 种,应激时间也增加到了 7 周,从而产生了不同的试验结果。Roussel 等^[39]发现绵羊孕晚期(分娩前 5 周)隔离应激可以增加 8 月龄子代的活跃性和探究行为。孕期应激对个体生理和各种行为反应的影响虽然也可能涉及其他神经内分泌途径,但是主要与 HPA 轴活性的延长或者增加有关,HPA 轴活性变化是海马体内糖皮质激素负反馈受损的结果,并且这种影响可能反应了进化上的适应性机制,子代中所增加的 HPA 轴优势将有利于其在竞争或环境应激情况下产生防御性行为反应^[58]。

2.3 对子代心血管功能和健康的影响

人类和动物研究表明,在胎儿发育过程中营养不足,母体应激和糖皮质激素过量暴露对子代的心血管代谢和神经内分泌功能产生永久的影响^[23,59]。母体孕期应激对绵羊子代心血管功能和健康影响的

研究模型以人工合成糖皮质激素模拟应激模型为主,其研究结果与人类流行病学研究结果类似,孕期应激所造成的子代胎儿生长环境的变化可以对子代终生健康产生不良影响。绵羊孕期糖皮质激素处理可以导致子代胎儿高血压,并伴随着血管阻力增加,温和型血氧不足和脑血流量降低^[60],且与子代成年期高血压相关^[61-62]。Dodic等^[63]首次描述了绵羊孕期应激对子代高血压的编程效应,绵羊妊娠27 d时用地塞米松处理48 h(0.28 mg/kg),发现尽管子代出生前后生长发育正常,但是子代4月龄时出现高血压并持续到18月龄。随后,Dodic等^[64]进一步研究母体孕早期地塞米松短暂暴露(11.5 mg/d,2 d)对子代其它心血管功能的影响,结果发现可以导致绵羊子代成年期高血压、左心室肥厚和心功能储备减少。Sloboda等^[65]研究发现绵羊孕期(妊娠104、111、118和124 d)倍他米松处理(0.5 mg/kg)可以增加2岁子代的基础胰岛素水平及肝葡萄糖-6-磷酸酶的活性,可能会使子代的新陈代谢模式发生长期变化。Blasio等^[66]在绵羊妊娠26 d时用地塞米松处理48 h(0.48 mg/h),发现子代公羊新陈代谢内稳态和胰岛素作用发生了变化,导致成年子代公羊葡萄糖稳态的改变,并诱导其产生高胰岛素血症。Sadowska等^[67]研究发现绵羊孕期单疗程(妊娠104~107 d期间,每12 h 6 mg,共注射4次)或多疗程(妊娠76~78 d至104~107 d期间,每周接受一次与单疗程相同的处理程序,共进行5个疗程)地塞米松处理,可以改变胎儿血脑屏障的分子组成,从而影响其功能。同时,有研究表明,母体皮质醇浓度调节子宫胎盘糖酵解代谢,产生用于子宫内的乳酸盐;孕期应激所导致的母体皮质醇浓度的升高,可以使胎盘组织以更高的速度和更长的时间来生产乳酸盐,从而对绵羊子代健康产生不利影响^[68]。此外,儿茶酚胺引起的子宫血流量减少也是将母体应激转移给绵羊胎儿的机制之一,特别是在胎儿糖皮质激素受体表达受限的孕早期,儿茶酚胺可能是孕早期应激对子代发育和健康编程的主要因素^[69]。

在特殊的妊娠时期,胎儿的肾脏发育似乎对糖皮质激素特别敏感。子宫内不利的发育环境能改变大鼠胎儿肾脏基因的表达,某些效应可能持续到成年期,导致子代某些疾病的发展^[70]。绵羊妊娠26~28 d用地塞米松处理48 h(0.48 mg/h),会造成7岁子代的肾元数量减少40%^[71],在妊娠80 d用倍他米松处理(0.17 mg/kg)也会产生类似的结果^[62];

妊娠80~81 d绵羊倍他米松处理(0.17 mg/kg)改变了6月龄子代肾素表达和分泌,但是对18月龄子代无影响^[72]。在出生前接触过量的糖皮质激素被认为是胎儿起源的成年疾病假说的关键机制^[73],这种在器官发育的关键时期受到的损害,永久地改变了器官系统的结构和功能^[74]。因此,孕期应激所造成的绵羊子代成年期高血压,其潜在机制可能是绵羊胎儿期肾脏发育模式发生了变化。

2.4 对子代神经元结构和相关基因表达的影响

孕期胎儿大脑增长速度很快,其典型特征是高通量的神经元连接。这种过快的增长速度使得胎儿大脑特别容易受到母体应激所产生的过量激素的影响。这些激素可能阻碍形成正确的神经连接并降低神经可塑性和神经递质活性,引起个体认知功能和行为的微妙变化。啮齿动物的研究表明,孕期应激对子代神经系统发育和行为有负面影响^[75],可以增加皮质边缘系统结构修饰,特别是海马区、前额叶皮层和杏仁核区域的结构修饰,包括树突棘形态和密度的改变^[76-77]。大脑中的神经元结构是由树枝状分支组成,其表面分布着高度特化的结构—树突棘,树突棘结构对应激敏感,其密度或形态变化是实现突触功能、突触可塑性和连通模式的关键要素^[78]。绵羊妊娠90~92 d时,胎儿皮质边缘结构形成,而孕晚期则是绵羊胎儿神经元生长的关键时期,也是大脑发育最易受影响的敏感时期^[79]。在绵羊孕晚期(妊娠94~143 d)利用多种厌恶事件对母体进行慢性应激处理,子代出生时收集大脑研究,发现子代海马CA1区树突棘密度增加,短粗型树突棘数量增加,前额叶皮质中基因*Rac1*(与大脑神经元树突形态相关)和基因*Nr1*(与大脑突触传递有关)表达量显著降低,杏仁核中基因*Dlg4*(与大脑神经元树突形态相关)表达量显著增加^[7]。Coulon等^[80]在绵羊分娩前5周对母体分别进行温和处理(GEN)和多种厌恶事件应激处理(AVS),发现与GEN子代相比,AVS子代1月龄时海马CA1区和前额叶皮层的锥体神经元树突棘密度增加,并且在海马CA1区蘑菇型树突棘数量减少,短粗型、细长型树突棘数量增加,前额叶皮质中基因*RhoA*(在脊柱形态发生中起重要作用)、*PURa*(与突触后小室形成有关)和*CPE*(与神经发育有关),以及海马中基因*PSD-95*(与树突棘成熟有关)表达量均显著降低。因此,树突棘密度和形态的变化与控制树突棘形态发育的基因表达变化有关。孕期应激的子代无论是在刚出生时,还

是在1月龄时,树突棘密度变化都有相似的结果,可以推测,1月龄子代树突棘密度的变化也许在刚出生时就已经存在。孕期应激对胎儿大脑结构的修饰也许反映了突出传递的重要功能变化,从而影响了随后的经验依赖型突触变化的进程,导致子代出现情感障碍^[65]。

树突棘密度和形态的变化对大脑皮质边缘结构的功能影响很大,树突棘是锥体神经元兴奋性突触的原发部位,其形态可塑性可能在重塑学习和记忆等高级大脑功能的神经回路中起着重要作用^[81],树突棘形态是兴奋性突触生理机能的重要调节因子^[82]。尽管孕期应激提高了树突棘的密度,但是减少了兴奋性突触的数量,因此,树突棘密度的增加可能是对神经元损失的适应性反应^[83]。孕期应激引起的树突棘密度变化改变了胎儿大脑的正常发育,影响胎儿发育初期大脑边缘结构的神经元回路。树突棘密度和形态的改变与以认知障碍为特征的神经发育异常有关^[84]。绵羊母体应激引起子代树突棘形态和密度的变化可能反映了突触传递的重要功能变化,并增加了子代的恐惧反应和认知能力障碍^[4,85]。此外,绵羊孕晚期(妊娠104、111、118和124 d)反复人工合成糖皮质激素(0.5 mg/kg)处理,可以延迟子代羔羊脑胼胝体轴突的髓鞘形成^[86],延缓星型胶质细胞和毛细血管紧密连接的成熟^[87],而胼胝体与个体更高层次的认知能力有关,其发育受损可能与子代的脑瘫、精神发育迟滞和注意力缺陷多动症等相关^[86]。孕期应激对胎儿大脑神经细胞形态的作用可能与胎儿所接触到的皮质醇的剂量和持续时间有关。Fujioka等^[88]研究发现对大鼠进行持续时间较长的应激时(自妊娠15~17 d开始,每天进行4 h应激),对胎儿下丘脑室旁核的神经元有神经毒性;然而持续时间较短的应激(自妊娠15~17 d开始,每天进行30 min应激)则可以促进大鼠胎儿大脑神经元的发育。

3 孕期应激的应对策略

除了利用绵羊模型之外,也有研究利用大鼠、豚鼠、猪等模型来揭示孕期应激如何影响子代终生健康轨迹的机制^[29,89-90]。孕期应激的后果可能是复杂和持久的,对子代表型的编程效应通常可以持续到子代成年,甚至可能传递更多代,因此需要能够实施行之有效的应对策略,来逆转或者减弱孕期应激对母体的影响以及对子代的编程效应。然而,目前仍

然没有公认的策略来应对孕期应激所带来的不良编程效应^[91]。一些研究试图利用动物饮食变化来逆转孕期应激^[92];另一些研究证实环境富集是可以减轻孕期应激对个体影响的有效应对策略^[93]。环境富集通常包括将动物安置在提供玩具和多样化饮食的环境中,从而产生丰富的认知、社交、运动和感官刺激,作为一种非侵入性应对策略来实施^[91]。环境富集能够通过基因表达的表观遗传调控来调节HPA轴活性、应激相关的行为特征和必需的免疫功能等^[94-96],由环境富集所引起的有益的内分泌和行为变化可能与生物体整个生命周期的表观遗传重编程相关,从而克服祖先和个体早期生命阶段的不良内分泌编程。研究表明:环境富集能够促进神经发生和突触发生,增加树突分支和树突棘密度,促进神经元连接;此外,环境富集可以改善学习和记忆,并保护由脑损伤或者应激所引起的认知缺陷^[97]。

环境富集是否能够逆转孕期应激对子代编程效应的研究主要以大鼠为研究对象,在家畜方面的研究较少;McCreary和Gerlinde^[91]综述了环境富集是否能成为一种有效的应对策略,来逆转孕期应激对大鼠、豚鼠子代的不良编程效应,研究发现尽管对孕期应激和环境富集进行研究的数量有限,但在所有研究中,环境富集似乎都能给孕期应激的动物带来有益的影响,可在很大程度上逆转孕期应激对子代行为、生理和分子等方面的不良编程;Brajon等^[98]研究了猪哺乳期(出生后1~20 d)环境富集是否能够逆转孕中期(妊娠39~45 d和59~65 d)混群应激的不良编程,发现哺乳期环境富集可以增加不同日龄仔猪(6、12、20、21、22、27 d)的探究行为,提高舒适度(仔猪躺卧时间更长),减少移动和争斗行为;断奶后去除环境富集对仔猪产生了负面影响,探究行为、玩耍行为(移动和争斗行为)减少,拱腹行为增加。但是,在出生后17 d进行社群隔离试验时则发现,环境富集可以增加仔猪的情绪反应(仔猪高音呼叫和逃逸企图更强),未发现哺乳期环境富集对仔猪早期应激的补偿作用。因此,环境富集能否成为逆转孕期应激不良编程效应的应对策略,仍需要进一步从动物的行为、生理和分子水平上进行研究,同时,也可以增加对断奶后环境富集的研究,因为孕期应激对子代行为的不良编程有延迟效应^[98]。

子代个体对环境富集响应的不同可能取决于产后环境富集实施的时间和类型,亲代抚育质量以及子代表型对孕期应激的弹性或易感性^[91]。“差异易

感性”模型表明,受应激不良影响最大的个体可能是从环境富集中受益最多的个体^[99]。未来对孕期应激编程的应对策略研究可以从环境富集着手,根据不同动物种类,不同的应激类型和实施时间来设计合适的环境富集实施方案,从行为、生理、表观遗传和神经解剖学等多层面研究,并要考虑到性别差异。此外,要有效地利用先进的基因组学技术,如表观基因组学,确定与孕期应激相关的表观遗传标记,通过环境富集等应对策略来逆转与应激相关的表观遗传变化。可以借鉴模式动物大鼠中的研究,探讨环境富集或者其他应对策略对绵羊孕期应激不良编程的逆转效果。

4 结 语

孕期应激所引起的母体糖皮质激素水平升高,与子代出生后内分泌功能、性情和认知能力的改变有关^[100]。绵羊人工合成糖皮质激素模型和母体应激模型对子代表型的影响存在一些差异,这些差异可能是由不同的试验方案所引起的,方案不同使得绵羊子代胎儿所接触的皮质醇剂量和持续时间不同。但孕期应激对胎儿的编程效应也有可能存在着其它激素调控的机制。在孕期应激模型中,应激反应伴随着多种内分泌变化,包括儿茶酚胺的释放、类固醇激素和生长因子的作用,这些也可能直接影响胎儿基因表达或通过改变胎盘代谢和调节子宫血流量和营养元素的重新分配而间接影响胎儿发育^[17]。母体不同妊娠时期应激对子代的编程效应也可能不同。绵羊母体应激模型多数以孕晚期模型为主,这可能是因为孕晚期与胎儿 HPA 轴、免疫活性细胞形成和大脑神经元生长密切相关。绵羊不同妊娠时期应激对子代的影响受应激类型、母体年龄以及所研究的子代年龄等因素影响,绵羊孕期应激对子代的影响可能存在长期效应,并对不同龄子代的生理、行为等影响各不相同,因此,连续研究(而不是仅仅选择子代某一年龄段来研究)孕期应激对绵羊子代不同年龄的发育编程具有重要意义。

总之,无论是人工合成糖皮质激素模型还是母体应激模型,绵羊孕期应激均可以对子代生长发育、行为、神经内分泌、基因表达和健康等产生影响。但是,目前绵羊孕期应激对子代影响的研究还不够深入,对孕期应激不良编程的应对策略研究较少,因此,未来绵羊孕期应激对子代编程效应的研究应该侧重于对子代基因表达、免疫功能、生产性能和母性

行为的影响等方面,特别是不同妊娠时期母体应激的比较研究和对子代影响的连续研究方面。同时,还要开展针对孕期应激不良编程的应对策略研究,特别是环境富集对绵羊孕期应激不良编程逆转效果的研究。此外,建议孕期应激模型可以多采用与生产管理措施相关的模型,比如隔离应激、由混群造成的社群应激等。绵羊孕期应激影响子代的福利和经济价值,因此,研究孕期应激对子代的编程效应,以及对孕期应激采取的应对策略,在绵羊的生产管理、动物福利和育种等方面均具有很重要的参考价值。

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