



间歇性限饲通过自噬改善小鼠卵巢功能的研究

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摘要: 本研究采用间歇性限饲(IF)的饲喂方法, 探究该种饮食方法对小鼠卵巢功能的影响及机制, 旨在为家畜繁殖管理提供理论依据。本研究采用8周龄体重相近的C57BL/6J雌鼠, 随机分为两组, 一组为正常饮食对照组(ND), 另一组通过“1天限饲(70%采食量)-1天自由采食”的循环模式建立间歇性轻度限饲(IMF)小鼠模型, 检测小鼠生长性能, 通过Western blot(WB)及免疫组化试验检测卵巢功能及自噬相关蛋白的表达。结果表明, IMF可显著降低料重比(82.85 ± 2.68 & 93.02 ± 7.40)和腹腔脂肪指数(1.49 ± 0.11 & 1.72 ± 0.19), 同时上调自噬标志物LC3 II/LC3 I (1.06 ± 0.12 & 0.89 ± 0.02)和生殖功能蛋白BMP-15 (1.05 ± 0.08 & 0.75 ± 0.10)、GDF-9 (0.53 ± 0.02 & 0.44 ± 0.02)。研究表明, IMF通过抑制mTOR通路($p\text{-mTOR/mTOR}$ 0.82 ± 0.10 & 0.97 ± 0.05)激活自噬, 进而改善卵巢功能。本研究首次揭示了IMF通过自噬途径促进卵巢功能的作用机制, 为家畜繁殖调控技术提供了一种潜在的非药物策略。

关键词: 间歇性限饲; 自噬; 卵巢功能; 家畜繁殖

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Intermittent Feed Restriction Improves Mouse Ovarian Function through Autophagy

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Abstract: This study adopted an IF feeding method to investigate the effects and mechanisms of this dietary approach on ovarian function in mice, aiming to provide a theoretical basis for livestock reproduction management. In this study, 8-week-old female C57BL/6J mice with similar body weights were randomly divided into two groups: one group served as the normal diet control group (ND), while the other group was subjected to a cyclic pattern of “1 day of restricted feeding (70% feed intake)-1 day of free feeding” to establish an intermittent mild fasting (IMF) mouse model. The growth performance of the mice was measured, and ovarian function as well as the expression of autophagy-related proteins were detected through Western blot (WB) and immunohistochemistry

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experiments. The results showed that IMF could significantly reduce the feed-to-gain ratio (82.85 ± 2.68 & 93.02 ± 7.40) and abdominal fat index (1.49 ± 0.11 & 1.72 ± 0.19). At the same time, the autophagy markers LC3 II /LC3 I (1.06 ± 0.12 & 0.89 ± 0.02) and reproductive function proteins BMP-15 (1.05 ± 0.08 & 0.75 ± 0.10) and GDF-9 (0.53 ± 0.02 & 0.44 ± 0.02) were up-regulated. The mechanism study showed that IMF activated autophagy by inhibiting mTOR pathway (p-mTOR/mTOR 0.82 ± 0.10 & 0.97 ± 0.05), and then improved ovarian function. This study is the first to elucidate the mechanism by which IMF enhances ovarian function through autophagy activation, offering a potential non-pharmaceutical strategy for developing reproductive regulation techniques in livestock.

Keywords: intermittent feed; autophagy; ovarian function; livestock reproduction

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随着畜牧产业向高效化、生态化方向发展,如何通过营养策略改善家畜繁殖性能已成为研究热点^[1]。间歇性限饲(IF)作为一种新兴饲养模式,在调节机体代谢^[2-3]、延缓衰老^[4-5]等方面表现突出,但其对雌性动物生殖功能的影响机制尚不明确,特别是在家畜繁殖领域的应用潜力亟待探索。自噬是细胞应对能量应激的重要机制,在卵泡发育过程中发挥关键作用^[6-7]。研究表明,适度自噬可维持卵母细胞质量,而过度激活则可能导致卵泡闭锁^[8-9]。在畜牧生产中,母猪等家畜常面临能量过剩导致的繁殖障碍问题,如卵泡发育不同步、受胎率下降等^[10]。目前主要通过外源激素调控^[11-12],但存在药物残留和成本高等问题。因此,开发基于自噬调控的非药物营养策略具有重要意义。

本研究以 C57BL/6J 小鼠为模型,创新性地采用“短期轻度限饲-正常饲喂”循环模式,系统研究间歇性轻度限饲(IMF)对卵巢功能的影响。通过解析自噬通路 with 生殖功能蛋白的调控关系,为理解能量

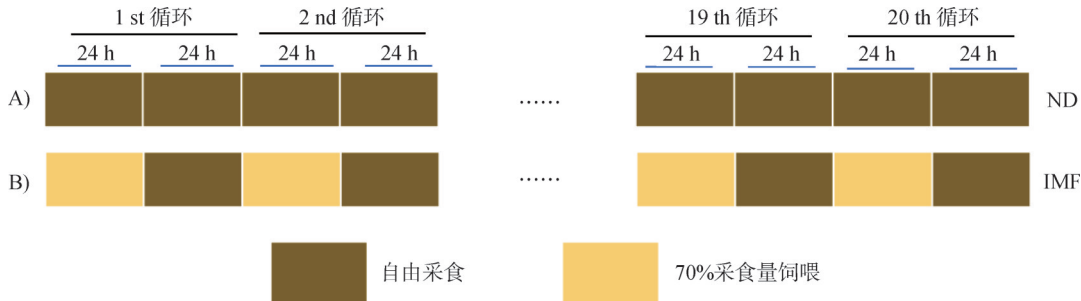
限制改善生殖功能的机制提供新见解。

1 材料与方法

1.1 动物模型

选取 8 周龄雌性 C57BL/6J 小鼠进行试验。每只小鼠单笼饲养,测定日均采食量,自由饮水,小鼠随机分为 2 组:正常饮食组(ND 组),小鼠自由进食;间歇性轻度限饲组(intermittent mild restricted feeding, IMF),以第 1 天饲喂日均采食量的 70%,第 2 天自由进食的饲喂模式,循环饲喂 20 个周期(图 1),试验完成后,收集小鼠卵巢并称重。

本研究中小鼠购自扬州比较医学实验动物中心,实验动物生产许可证号:SCXK(苏)2022-0009;小鼠饲养设施的环境条件符合中国国家标准《实验动物环境及设施》(GB 14925—2001)对屏障动物实验设施的有关标准,动物饲养管理和动物实验操作符合相关法规的要求。



A. ND 组饲喂模式;B. IMF 组饲喂模式

A. Normal diet (ND) group regimen; B. Intermittent mild feed (IMF) group regimen

图 1 小鼠饲喂模式

Fig. 1 Mouse feeding regimens

1.2 生长性能试验

称量各组小鼠初始体重和终体重,绘制生长曲线。试验期间每天观察各组小鼠的健康状况,每天同一时间测量各组总采食量,计算料重比。称量各组小鼠主要脏器的重量,并计算脏器指数。

脏器指数 $\%$ =脏器重量/体重 $\times 100\%$ ^[13]。

1.3 WB检测自噬相关蛋白和生殖功能相关蛋白的表达

提取各组卵巢组织总蛋白。通过聚丙烯酰胺凝胶电泳(60 V电泳30 min后转90 V电泳60 min)和膜转移(60 V转膜120 min),以 β -actin(sc-48166, SANTA, USA)作为内参蛋白,评估自噬相关蛋白:微管相关蛋白轻链3(microtubule-associated protein 1 light chain 3, LC3; 14600-1-AP, Proteintech, USA)、螯合体1(SQSTM1/p62; ab233207, Abcam, USA)、哺乳动物雷帕霉素靶蛋白(ammalian target of rapamycin, mTOR; 66888-1-lg, Proteintech, USA)、磷酸化mTOR(phospho-mTOR, p-mTOR; 67778-1-lg, Proteintech, USA)。此外,评估生殖功能相关蛋白,包括卵泡刺激素受体(follicle-stimulating hormone receptor, FSHR; 18982-1-AP, Proteintech, USA)和骨形态发生蛋白-15(bonemorphogenetic protein-1, BMP-15; 22665-1-AP, proteintech, USA)的表达。通过计算目的条带与相应内参条带灰度值的比值来确定各目的蛋白的相对表达量^[14]。

1.4 免疫组织化学检测

收集的卵巢组织在4%多聚甲醛中室温固定5 h,随后用PBS洗涤样品,脱水,透明,包埋后切片。切片经酒精二甲苯复水后流水冲洗,抗原修复,5% BSA封闭,过夜孵育一抗,洗涤后孵育二抗,DAB显色后苏木素染色,脱水透明封片^[15-16]。利用免疫组化检测卵巢颗粒细胞中自噬相关蛋白mTOR、p-mTOR、p62、LC3B(ab229327, Abcam, USA)的表达。此外,利用颗粒细胞中的BMP-15和FSHR以及卵母细胞中的生长分化因子-9(growth differentiation factor-9, GDF-9; ab254323, Abcam, USA)来评估卵巢功能。

1.5 统计分析

数据以“ $\bar{x}\pm s$ ”表示,使用GraphPad Prism 10.2.0(GraphPad Software, LA Jolla, CA, USA)进行数据收集和分析,组间采用单因素方差分析,判断标准以 $P<0.05$ 为差异显著, $P<0.01$ 为差异极显著。

2 结果

2.1 小鼠生长性能检测

对小鼠健康状态进行评估,IMF组小鼠与ND组相比无明显异常。在造模期间限饲组小鼠表现出体重先下降再上升的趋势,经20个限饲循环后ND组与IMF组终体重无显著差异(21.38 ± 0.79 g & 22.34 ± 0.66 g, $P>0.05$);2组小鼠的总采食量存在显著差异(102.20 ± 1.42 g & 97.93 ± 2.18 g, $P<0.05$),料重比存在显著差异(93.02 ± 7.40 & 82.85 ± 2.68 , $P<0.05$)(图2)。

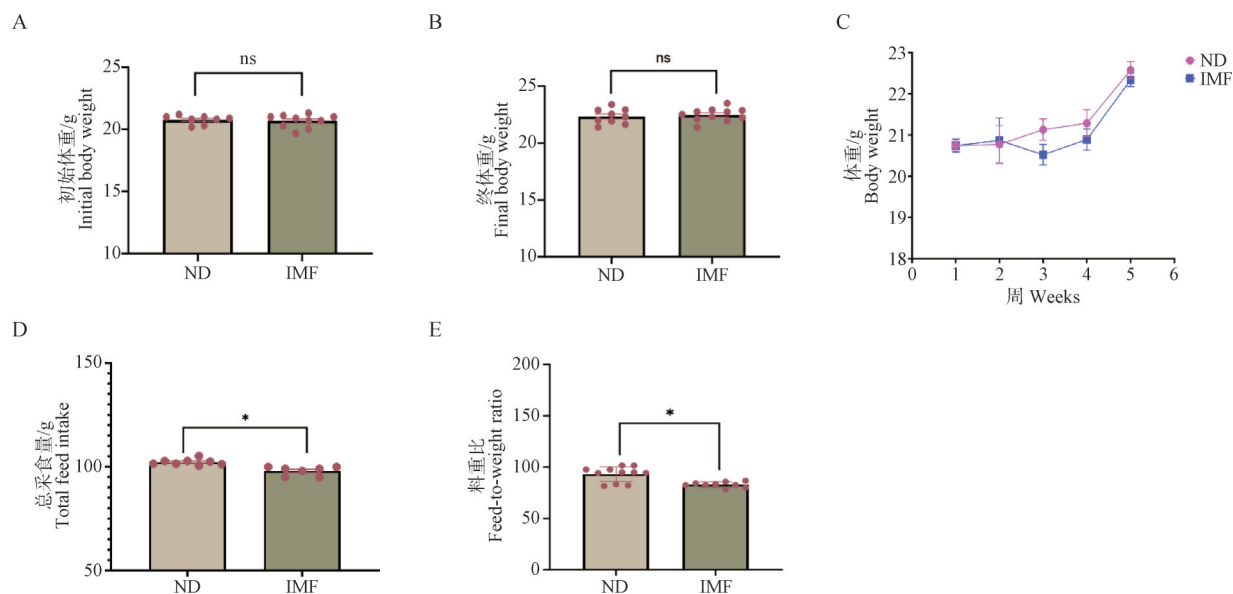
小鼠造模结束后脏器指数结果显示,两组间心、肝、脾、肺、肾和卵巢脏器指数均无显著性差异($P>0.05$),卵巢组织外部形态及大小无明显差异。与ND组相比,IMF组小鼠的腹腔脂肪脏器指数显著降低(1.72 ± 0.19 & 1.49 ± 0.11 , $P<0.05$);而腓肠肌脏器指数则极显著升高(0.52 ± 0.02 & 0.61 ± 0.05 , $P<0.01$)(图3)。

2.2 自噬水平检测

以 β -actin为内参,Western blot检测卵巢自噬及相关通路蛋白,结果如图4所示,IMF组LC3 II/LC3 I相对表达量显著高于ND组(1.06 ± 0.12 & 0.89 ± 0.02 , $P<0.05$);与ND组相比,IMF组小鼠p62蛋白相对表达量极显著降低(0.96 ± 0.02 & 0.82 ± 0.01 , $P<0.01$),p-mTOR/mTOR相对表达比值显著降低(0.97 ± 0.05 & 0.82 ± 0.10 , $P<0.05$)。免疫组化检测结果显示,在卵泡组织的颗粒细胞中可检测到自噬及通路相关蛋白的表达,LC3B、p62、p-mTOR/mTOR在卵泡组织颗粒细胞中的相对表达量变化趋势与Western blot分析结果一致(图5)。

2.3 生殖功能相关蛋白检测

利用Western blot检测卵巢功能相关蛋白,结果如图6所示,ND组和IMF组小鼠卵巢中FSHR蛋白相对含量无显著性差异(1.14 ± 0.02 & 1.15 ± 0.06 , $P>0.05$);IMF组BMP-15蛋白相对含量极显著高于ND组(1.05 ± 0.08 & 0.75 ± 0.10 , $P<0.01$)。免疫组化检测卵巢组织中生殖功能相关蛋白(图7),与ND组相比,FSHR和BMP-15在卵巢颗粒细胞中的相对表达量与Western blot检测结果一致;IMF组GDF-9蛋白相对表达量极显著升高(0.44 ± 0.02 & 0.53 ± 0.02 , $P<0.01$)。

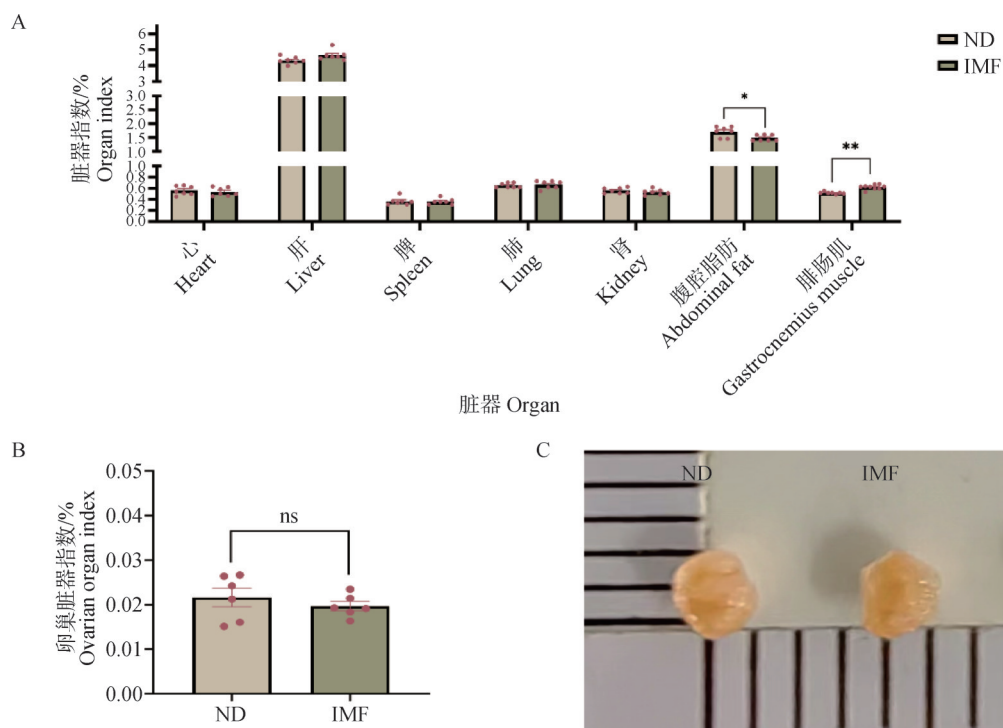


A. 小鼠初始体重; B. 间歇限饲20个周期后小鼠终体重; C. 间歇限饲期间小鼠体重曲线; D. 小鼠总采食量; E. 小鼠的料重比。ns. $P > 0.05$; *. $P < 0.05$; **. $P < 0.01$, 下同

A. Initial body weight of mice; B. Final body weight after 20 cycles of intermittent fasting; C. Body weight curve during intermittent fasting; D. Total feed intake of mice; E. Feed-to-gain ratio of mice. ns. $P > 0.05$; *. $P < 0.05$; **. $P < 0.01$, the same as below

图2 小鼠生长性能及料重比

Fig. 2 Growth performance and feed conversion ratio of mice

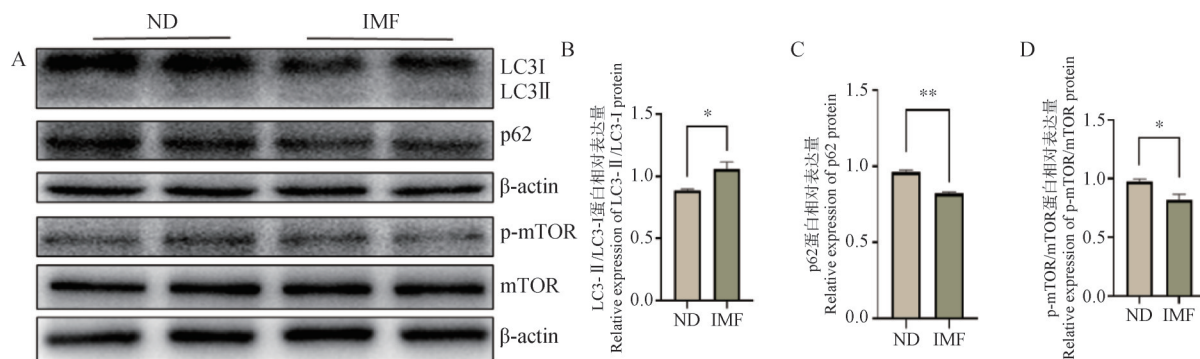


A. 小鼠主要脏器指数; B. 小鼠卵巢脏器指数; C. 小鼠卵巢形态和大小

A. Major organ indices of mice; B. Ovarian organ index of mice; C. Ovarian morphology and size of mice

图3 小鼠主要脏器指数

Fig. 3 Organ indices of mice

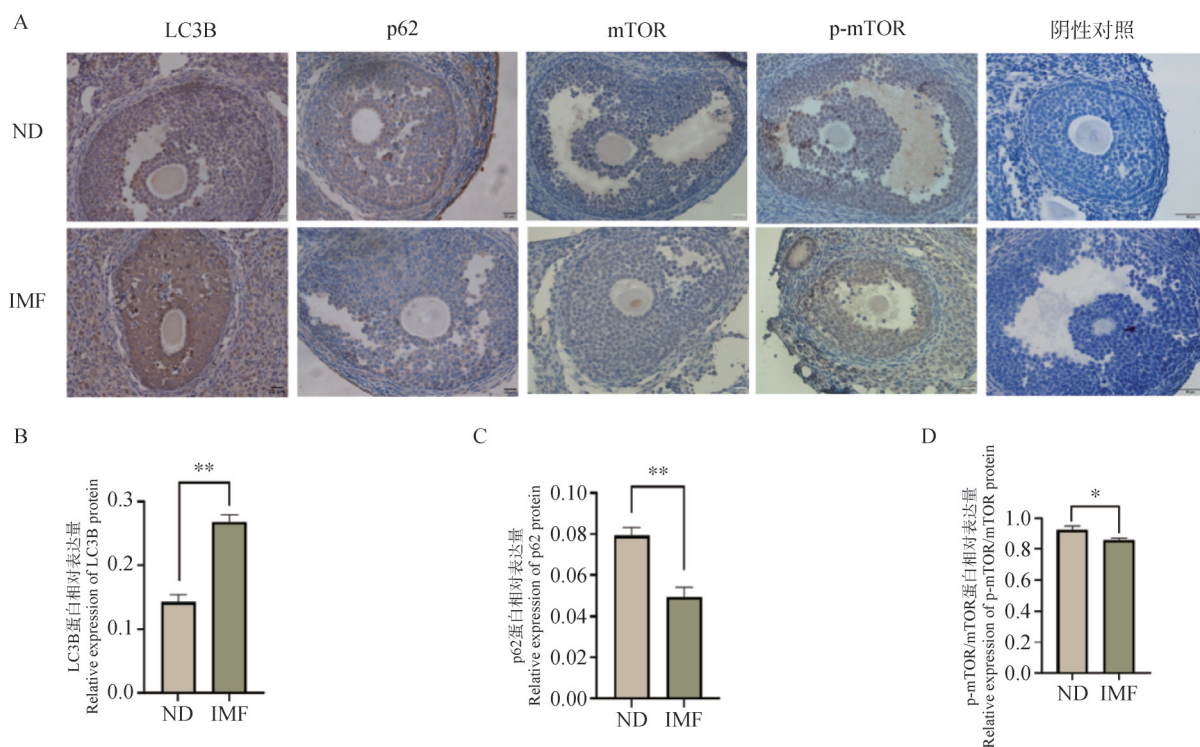


A. 小鼠自噬及通路相关蛋白印记; B. LC3-II/LC3-I 蛋白印迹灰度分析; C. p62 蛋白印迹灰度分析; D. p-mTOR/mTOR 蛋白印迹灰度分析

A. Immunoblotting of autophagy and pathway-related proteins in mice; B. Grayscale analysis of LC3-II/LC3-I protein immunoblotting; C. Grayscale analysis of p62 protein immunoblotting; D. Grayscale analysis of p-mTOR/mTOR protein immunoblotting

图4 Western blot检测自噬及通路相关蛋白

Fig. 4 Autophagy and pathway-related proteins detected by Western blot



A. 各组卵巢组织自噬相关蛋白免疫组化图片(400 $\times$); B. LC3B 的相对表达量; C. p62 的相对表达量; D. p-mTOR/mTOR 的相对表达量

A. Immunohistochemical images of autophagy-related proteins in ovarian tissues from each group (400 $\times$); B. Relative expression of LC3B; C. Relative expression of p62; D. Relative expression of p-mTOR/mTOR

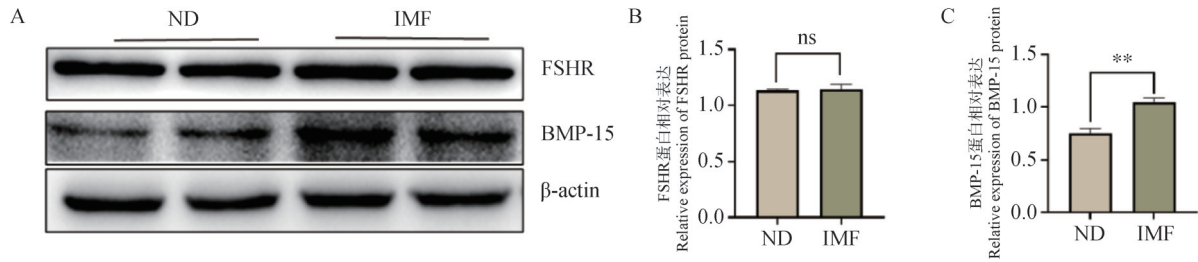
图5 免疫组化检测小鼠卵巢颗粒细胞自噬及通路相关蛋白

Fig. 5 Immunohistochemical detection of autophagy and pathway-related proteins in mouse ovarian granulosa cells

3 讨论

间歇性限饲(intermittent restricted feeding, IF)

作为一种周期性能量限制的饲喂模式^[17],通过在特定时间内禁食或大幅减少能量摄入,随后恢复正常饮食,以实现代谢和生理上的益处,已被证明对体

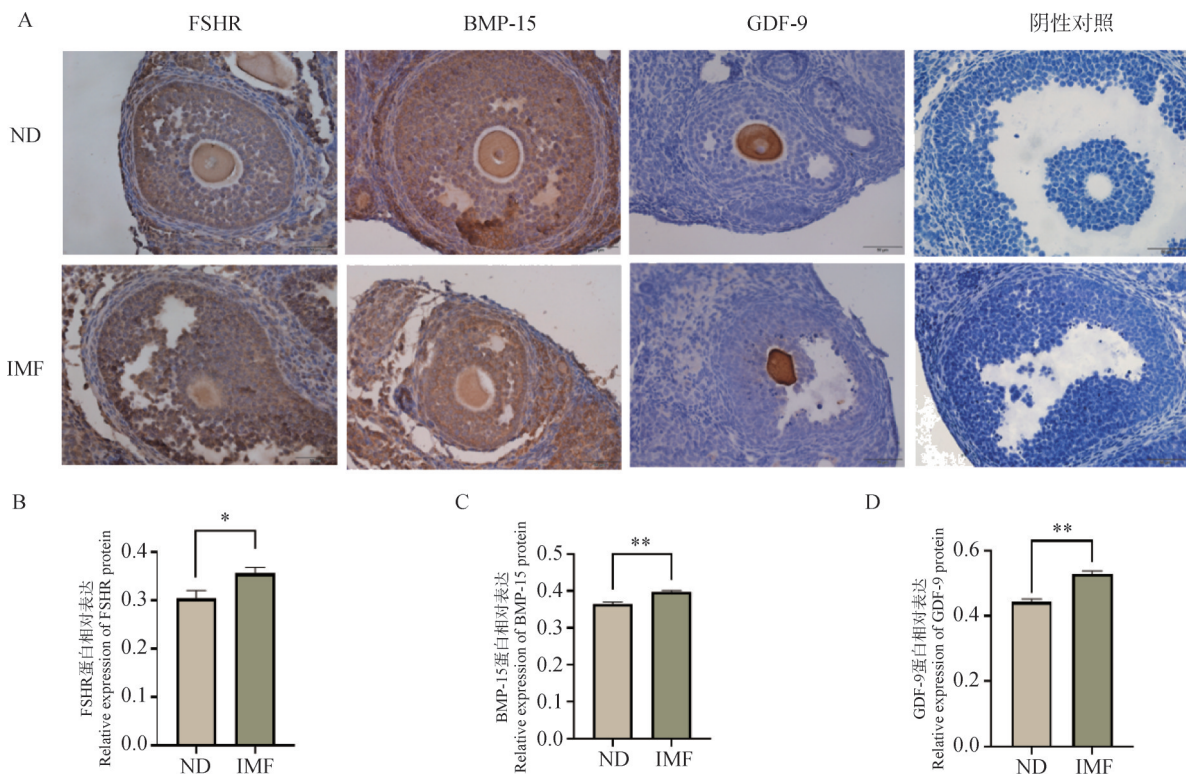


A. 小鼠卵巢组织中生殖功能相关蛋白印记; B. FSHR 蛋白印记灰度分析; C. BMP-15 蛋白印记灰度分析

A. Immunoblotting of reproduction-related proteins in mouse ovarian tissue; B. Grayscale analysis of FSHR protein expression; C. Grayscale analysis of BMP-15 protein expression

图 6 Western blot 检测生殖功能相关蛋白

Fig. 6 Western blot analysis of reproduction-related proteins



A. 各组卵巢组织中生殖功能相关蛋白免疫组化图片 (400 $\times$); B. FSHR 相对表达量; C. BMP-15 相对表达量; D. 卵母细胞中 GDF-9 相对表达量

A. Representative immunohistochemical images of reproduction-related proteins in ovarian tissue across experimental groups (400 $\times$); B. Relative expression level of FSHR; C. Relative expression level of BMP-15; D. Relative expression level of GDF-9 in oocytes

图 7 免疫组化检测小鼠卵巢颗粒细胞和卵母细胞生殖功能相关蛋白

Fig. 7 Immunohistochemical (IHC) analysis of reproduction-related proteins in mouse ovarian granulosa cells and oocytes

重减轻、胰岛素敏感性等都有积极影响,其对生殖的影响机制日益受到关注,利用营养控制策略来提升家畜繁殖效率也可以缓解我国近年来一直面临高蛋白饲料如豆粕“卡脖子”问题^[18-21]。本研究采用“短期轻度限饲(1天)后正常饮食(1天)”的策略,提

出的 IMF 方案(“1天 70% 采食量+1天自由采食”多周期)与传统的持续性限饲相比,IMF 模式更符合动物福利要求,且能避免过度应激。本研究从机制上剖析了 IMF 对卵巢功能的采食依赖性影响,揭示了代谢适应和卵泡稳态之间的微妙平衡。饲料

补偿效应的评估通常基于体重变化率、脏器指数及采食量的测定数据,通过计算饲料转化效率进行综合判断^[22]。本研究发现,间歇性轻度限饲(IMF)组小鼠表现出良好的健康状况,骨骼肌量增加,腹部脂肪量减少,这些都与采食量和料重比减少有关。限饲可诱导机体多个组织发生自噬,进而影响其功能。为评估间歇性轻度限饲的效果,本研究检测了自噬过程中的关键蛋白质 LC3 和 p62^[23-25],mTOR 的相对活性可以决定自噬诱导的程度,抑制 mTOR 的活性从而促进自噬的发生^[26-28],前期研究发现血清饥饿胁迫能诱发基于 mTOR 通路的自噬,并能调控骨骼肌卫星细胞的代谢和自噬过程中的关键蛋白质 LC3 和 p62 分化功能^[29-30]。本研究发现,间歇性限饲与自噬活性增加相关,自噬活性增加有助于产生有益的代谢效应,并增强生殖健康^[31]。为了从分子水平评估卵巢功能的指标,本研究检测了生殖功能密切相关蛋白 FSHR、BMP-15 和 GDF-9 的表达,其中 FSHR 主要由卵巢颗粒细胞分泌,颗粒细胞在原始卵泡的起始和生长过程中发挥重要的调控作用,其表达水平与颗粒细胞分化、卵泡闭锁和成熟密切相关^[32-34]。BMP-15 和 GDF-9 在卵巢组织中表达,协同调节卵母细胞的成熟和增殖以及颗粒细胞的分化^[35-38]。本研究证实,间歇性轻度限饲(IMF)可通过 mTOR-自噬通路显著提升卵巢功能,这一发现为家畜繁殖管理提供了新的技术思路。

在后续研究中,本实验室聚焦于间歇性轻度限饲对生殖力的改善,初步结果证明限饲组小鼠拥有更高的原始卵泡数和总卵泡数,且排卵数及卵母细胞成熟率更高,体外受精结果显示,限饲组小鼠囊胚率显著高于正常组,且自然交配后妊娠率、产仔数也更高(待发表数据)。现有家畜饲养中,已有研究表明营养控制对家畜的发情、排卵有重要影响^[39-40]。本研究证实,IMF 可内源性上调生殖功能相关蛋白,从分子水平证明了 IMF 对生殖的促进作用,基于上述研究,利用“营养-自噬”通路提升家畜繁殖力的方案展示出较好的可行性,可以部分替代激素使用,这对推动高效生态养殖具有重要意义。

4 结 论

本研究揭示间歇性轻度限饲(IMF)在改善代谢健康的同时,通过 mTOR-自噬通路显著提升卵巢功能,证实 IMF 在代谢适应与卵泡稳态间建立良性

平衡,为生殖管理提供了创新性干预策略。

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