

何晓桦, 唐小鹏, 招华兴, 等. GALANIN 家族成员对动物生殖功能的调控作用 [J]. 畜牧与兽医, 2026, 58 (10): 140-146.

He X H, Tang X P, Zhao H X, et al. Regulatory roles of GALANIN family members in animal reproduction [J]. Animal Husbandry & Veterinary Medicine, 2026, 58 (10): 140-146.

GALANIN 家族成员对动物生殖功能的调控作用

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摘要: 畜禽生殖功能的精准调控是保障养殖效益、推动优良品种繁育的核心环节, 该过程依赖下丘脑-垂体-性腺 (HPG) 轴与局部信号通路的协同, 甘丙肽 (GAL)、甘丙肽样肽 (GALP)、斯佩辛 (SPX) 同属神经肽 GALANIN 家族, 三者共享 GAL 受体, 但分子特征与功能定位存在差异: GAL 以“中枢增强 HPG 轴信号+外周调控生殖器官收缩”为核心, 促进促性腺激素释放激素 (GnRH) 与促性腺激素分泌调控母畜护仔、泌乳等与生产相关的母性行为, 同时直接促进子宫平滑肌收缩; GALP 作为瘦素下游关键因子, 激活 GnRH 神经元, 是衔接畜禽营养代谢状态与繁殖性能的关键桥梁; SPX 则通过抑制 GnRH 分泌及性腺功能, 在能量缺乏时抑制生殖以保存能量。本文系统综述三者的分子结构、受体系统及生殖调控机制, 阐明其作用模式, 为针对畜禽繁殖障碍、早产、营养性生殖异常等问题进行临床干预提供理论依据与潜在靶点。

关键词: 甘丙肽; 甘丙肽样肽; 斯佩辛; 生殖调控; 子宫收缩

中图分类号: S814.8 文献标志码: A 文章编号: 0529-5130(2026)10-0140-07

Regulatory roles of GALANIN family members in animal reproduction

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Abstract: Precise regulation of reproductive function in livestock and poultry is a crucial factor in ensuring breeding efficiency and promoting the propagation of superior breeds. This process relies on the coordinated interaction between the hypothalamic-pituitary-gonadal (HPG) axis and local signaling pathways. The neuropeptides galanin (GAL), galanin-like peptide (GALP), and spexin (SPX), all belonging to the GALANIN family, share GAL receptors but differ in molecular characteristics and functional localization. GAL primarily functions by centrally enhancing HPG axis signaling and peripherally regulating reproductive organ contractions. It amplifies the secretion of gonadotropin-releasing hormone (GnRH) and gonadotropins, thereby modulating maternal behaviors such as offspring protection and lactation in female livestock. Additionally, GAL directly promotes uterine smooth muscle contraction. As a key downstream factor of leptin, GALP activates GnRH neurons and serves as a critical link connecting nutritional and metabolic status with reproductive performance in livestock and poultry. In contrast, SPX suppresses GnRH secretion and gonadal functions, inhibiting reproduction under conditions of energy deficiency to conserve energy. This article systematically reviews the molecular structures, receptor systems, and reproductive regulatory mechanisms of these three neuropeptides. It further elucidates their modes of action, aiming to provide a theoretical basis and potential targets for clinical intervention of issues such as reproductive disorders, premature birth, and nutrition-related reproductive abnormalities in livestock and poultry.

Keywords: GALANIN; galanin-like peptide; spexin; reproductive regulation; uterine contraction

生殖调控是畜禽物种延续与畜牧生产提质增效的核心生理过程, 覆盖配子发生、受精、胚胎发育至妊

娠结局全链条, 任一环节失衡均可能引发排卵障碍、久配不孕、胚胎早期死亡、早产等繁殖问题, 不仅威胁畜禽群体存续, 更直接影响养殖经济效益、优良品种扩繁及畜禽群体健康。生殖功能的精准调控是脊椎动物繁衍的核心保障, 其依赖于下丘脑-垂体-性腺 (hypothalamic-pituitary-gonadal, HPG) 轴为主的神

收稿日期: 2025-12-07; 修回日期: 2026-07-28

基金项目: 岭南现代农业实验室自主科研项目 (NT2025004)

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用。甘丙肽 (galanin, GAL), 甘丙肽样肽 (galanin-like peptide, GALP), 斯佩辛 (spexin, SPX) 均为进化保守的神经肽 GALANIN 家族成员, 通过选择性地和各种组织中的 GAL 受体结合发挥不同生物学功能, 甘丙肽受体 (galanin receptor, GALR) 由 GALR1、GALR2、GALR3 组成。GAL、GALP、SPX 均在下丘脑广泛分布, 并且参与生殖内分泌平衡的调节。目前关于 3 种神经肽的功能均已报道, 包括能量平衡、体重调节、葡萄糖稳态、炎症、认知和情绪等方面^[1-2], 但针对其生殖调控作用的分子机制及养殖应用价值的系统梳理仍较匮乏, 制约了其在解决实际养殖繁殖问题中的转化应用。本文旨在系统综述 GAL、GALP、SPX 在畜禽生殖调控中的基础作用, 解析其分子机制与研究进展, 为畜禽繁殖障碍的精准干预、繁殖性能提升技术研发提供理论参考。

1 GAL 家族成员

1.1 GAL

GAL 是一种由 29~30 个氨基酸组成的神经肽, 最早于 1983 年从猪肠道提取物中分离得到, 并且因其氨基末端甘氨酸和羧基末端酰胺基氨基酸而得名^[3]。后续在大鼠、人、鹌鹑等动物中均检测到 GAL, 除了人 GAL 由 30 个氨基酸组成, 其余物种 GAL 均由 29 个氨基酸组成, 并且不同物种 GAL 的氨基酸序列相似度高达 90% (图 1)。这种在物种间存在的高度保守性说明 GAL 具有生物学作用^[1]。目前 GAL 已被证明存在于许多脊椎动物神经系统和外周组织中, 下丘脑、脊髓和胃肠道、泌尿生殖道等均有发现 GAL 的表达^[4-6]。GAL 可以调节能量代谢、与

生殖相关的神经内分泌活动和肠道收缩等作用^[4,7-8]。GAL 通过激活已知受体 GALR1、GALR2、GALR3 而发挥作用^[9-11]。

1.2 GALP

GALP 是 GAL 家族成员的另一个神经肽, 最早是从猪下丘脑分离得到。该肽有 60 个氨基酸残基和 1 个未修饰的 C 端, 其中 GALP (9~21 aa) 的氨基酸序列与 GAL (1~13 aa) 完全相同 (图 1)^[12]。此外, GALP 在人、猪、大鼠、小鼠中具有高度的序列一致性。GALP 依次对 GALR3、GALR2、GALR1 表现出高亲和力, 并且 GALP 对 GALR2 的亲和力较 GAL 对 GALR2 的亲和力高^[13]。GALP mRNA 和 GALP 蛋白多表达于下丘脑中, 且与 GAL 相比, GALP 在中枢神经系统中的分布受限^[14-15]。已有大量证据证明, GALP 深度参与能量代谢和生殖调节^[16-19]。

1.3 SPX

SPX 又被称为神经肽 Q, 最早是通过生物信息技术进行数据挖掘被发现和证实^[20-21]。通过系统发育和共系分析发现, SPX 与 GAL 具有共同的进化祖先, 并被归类为 GAL 家族成员^[22]。SPX 和 GAL 成熟肽序列的高度同一性进一步揭示了这一点。该神经肽由 14 个氨基酸组成, 在哺乳动物和非哺乳动物中高度保守 (图 1)。它在不同的组织器官中广泛表达, 其中包括下丘脑、胃肠道、肌肉、卵巢等不同部位^[23-25]。同时, SPX 具有不同的生理功能, 包括参与生殖功能调节、骨骼肌代谢、平滑肌收缩等^[25-27]。为激活以上功能, SPX 能结合 GALR2 和 GALR3, 但却不能结合 GALR1^[28]。

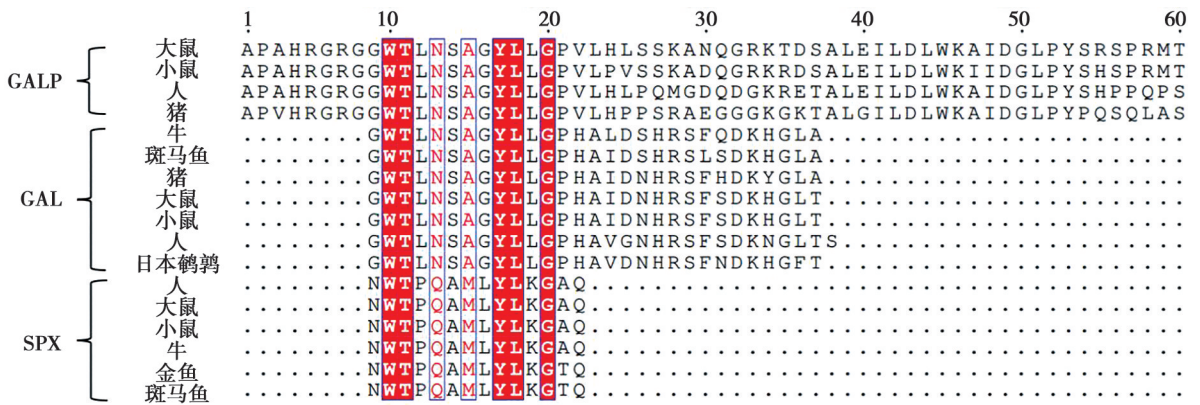


图 1 不同动物 GALP、GALANIN、SPEXIN 成熟肽序列的序列比对

2 GAL、GALP、SPX 介导的生殖调控

GAL、GALP 和 SPX 通过 HPG 轴的中枢调控和外周作用于生殖器官两种通路实现对生殖功能的调

控, 但三者的作用方式和效果不同。

2.1 GAL 是生殖信号的“增强者”与“执行者”

在中枢神经系统中, GAL 主要集中表达于下丘脑弓状核 (arcuate nucleus of the hypothalamus,

ARC), 下丘脑室旁核 (paraventricular nucleus of the hypothalamus, PVN) 和内侧视前区 (medial preoptic area, MPOA) 等与生殖调控密切相关的核团^[29-31]; 而在外周组织中, 其广泛分布于脊髓、卵巢、睾丸、子宫平滑肌以及输卵管等^[1,30]。这表明 GAL 是生殖系统中必不可少的调节因子之一, 其表现在中枢内分泌激素调控以及外周生殖功能调控上。

2.1.1 中枢层面对内分泌的调控作用

中枢神经系统中对生殖的调控是由 HPG 轴控制的, 下丘脑促性腺激素释放激素 (GnRH) 表达神经元位于该系统的顶端。GAL 免疫反应与表达 GnRH 神经元共定位于下丘脑中, 并且随着雌性大鼠发情期到来, 共表达 GnRH mRNA 的神经元中 GAL mRNA 的含量显著提高 2 倍^[32-33]。已有证据表明, GAL 参与控制 GnRH 的释放^[32-34]。大鼠 GAL 在体外以剂量依赖的方式刺激 GnRH 以及前列腺素 E₂ (prostaglandin E₂, PGE₂) 的释放。在雌性啮齿类和灵长类动物中, GAL 可以通过靠近 GnRH 的神经元直接作用于 GnRH 细胞, 也可以在排卵前促黄体素 (LH) 激增的时刻, 介导雌二醇 (E₂) 通过激活 GnRH 神经元中的 GALR1 和雌激素受体 α (estrogen receptor alpha, ER α) 发挥对 GnRH 神经元的正反馈作用^[33-35]。此外, GAL 可以通过调控 GnRH 的上游关键因子 - kisspeptin 和神经肽 Y (neuropeptide Y, NPY) 以达到间接调控 GnRH 分泌信号的效果^[36-37]。

在垂体水平上, GAL 可以直接调节促性腺激素 LH 释放或协同 GnRH 刺激 LH 的合成和释放^[38-39]。体外试验证明, 将 GAL 与大鼠垂体前叶细胞共培养, GAL 以剂量依赖方式刺激 LH 分泌, LH 的分泌量增加了 3~4 倍; 将 GAL 与 GnRH 共同孵育垂体细胞, LH 的分泌量较单独使用 GnRH 显著增加^[38-40]。在雄性大鼠中, GAL 在 T 的合成和功能方面也存在调节作用, GAL 显著增强人体绒毛膜促性腺激素 (hCG) 诱导的 T 释放, 并且这一作用受到 galantide (一种 GAL 拮抗剂) 的抑制, 说明这种增强作用是由 GAL 特异性介导的^[41]。同时, GAL 对催乳素也具有调控作用, GAL 基因敲除小鼠垂体催乳素 mRNA 及蛋白水平分别降低了 30% 和 40%, GAL 的过表达小鼠则会出现催乳素过度分泌的现象。在生理状态下, 这种调控关系在妊娠与泌乳期尤为突出^[42-43]。GAL 敲除雌鼠首次妊娠时因催乳素分泌不足, 出现乳腺发育失败与泌乳缺失^[42]。

2.1.2 外周层面对生殖行为的调控作用

2.1.2.1 子宫收缩

GAL 对子宫平滑肌收缩的调控是其外周生殖功能的核心体现。GAL 可以不依赖于神经传导和激素

调控, 直接诱导子宫平滑肌收缩^[44]。在大鼠中, GAL 通过 GAL 受体激活钙信号通路, 一方面促进细胞膜上电压门控钙通道开放, 增加外源性钙离子内流增加; 另一方面刺激钙离子从储存细胞内释放, 最终导致子宫收缩强度与频率增加^[45]。此外 GAL 还可以通过提高子宫平滑肌对钙离子的敏感性来诱导大鼠子宫平滑肌收缩^[45]。在猪炎症子宫中也反映出 GAL、GALR1 和 GALR2 参与对炎症子宫的收缩活性的调节^[46]。

在禽类中, GAL 的外周作用表现为调控输卵管功能。鹌鹑的子宫、阴道、输卵管中高度表达 GAL 受体, 在鹌鹑发育过程中, 输卵管中 GAL 受体的数量增加, GAL 直接作用于成熟的子宫和阴道促进该区域平滑肌收缩, 推动成熟卵子在输卵管内的运输与蛋壳形成。这也是 GAL 能提高鹌鹑产蛋率的关键机制, 外源性注射 GAL 可显著诱导鹌鹑产卵, 在注射 GAL 后 5 min 内能观察到有效的鹌鹑产卵情况^[47-48]。

2.1.2.2 母性行为

GAL 是母性行为精准调控的核心分子枢纽, 其作用以内侧视前区 (MPOA) 为核心, 整合激素信号与神经环路实现对母性关怀的全方位调控^[49]。MPOA 的 GAL 阳性神经元是雄性和雌性母性行为的关键开关^[50-52]。光遗传学激活该类神经元可使处女雄鼠抑制幼崽攻击并诱导养育行为, 而基因敲除该类神经元会导致小鼠幼崽取回、梳理等核心母性行为完全消失^[51,53]。这一调控依赖妊娠激素介导的 GAL 神经元产前重塑: 妊娠期雌激素通过激活 ER α 降低 GAL 神经元的膜电位, 选择性增强了对幼崽刺激有反应的 GAL 神经元的敏感性, 使得幼崽相关刺激 (如气味、叫声) 能更有效地触发动作电位并强化神经元对特定信号的捕捉能力, 并且使母体能够快速区分幼崽与其他无关刺激; 黄体酮借助黄体酮受体促进 GAL 神经元树突形成, 增加兴奋性突触连接密度, 使幼崽信号能更高效传递, 孕晚期小鼠衔幼崽潜伏时间从 477.9 s 缩短至 37.9 s^[50,54]。该调控机制具有跨物种保守性, 鱼类视前区 GAL 神经元促进其将后代放入口腔内的护幼行为^[55-56]。

2.1.2.3 性行为调控

GAL 在性行为调控中发挥不可或缺的作用。在雄性大鼠中, 脊髓腰骶段的 GAL 神经元的激活是射精行为的必要条件, 使用光遗传学和电生理试验证实这些神经元通过单突触连接投射至球海绵体肌运动神经元, 增强神经元兴奋性, 促进交配时的射精反射^[6,57]。此外, GAL 不仅执行射精反射, 还参与性唤起的中枢调控, 在雄性大鼠内侧视前核 (medial preoptic nucleus, MPN) 微量注射 GAL, 可剂量依赖

性增强交配行为和交配频率^[6,58]。在雌性大鼠中, MPN 注射 GAL 可增强其脊柱前凸和主动求偶的性行为^[59]。

2.2 GALP 是代谢-生殖轴的“桥梁”

与 GAL 的中枢与外周均广泛分布不同, GALP 主要在中枢神经系统中分布, 其中下丘脑弓形核 (arcuate nucleus of the hypothalamus, ARC) 和 MPOA 分布着大量 GALP 免疫反应纤维^[60]。因此, 其调控作用以中枢激活为主, 同时兼顾青春期和性行为调控, 在代谢-生殖平衡中发挥着不可或缺的作用。

2.2.1 内分泌调控

当神经元被激活时, Fos 蛋白会在细胞核中表达, 通过 Fos 免疫反应性定量分析显示, 与 GAL 相比, GALP 在布罗卡斜带核水平支 (horizontal limb of the diagonal band of broca, DBB), 视前区尾部, ARC 和正中隆起 (median eminence, ME) 诱导的与 GnRH 相关的 Fos 阳性细胞明显增多, 这提示 GALP 也是 GnRH 释放激活因子之一^[61-62]。下丘脑 GALP 神经元通过直接激活 GnRH 神经元刺激 GnRH 释放^[63-64], 体外试验显示, 向大鼠下丘脑视前区微注射 GALP, 可使 GnRH 神经元放电频率增加, LH 血清水平在 30 min 内升高 5 倍^[62]。

在垂体层面, GALP 可以直接作用于促性腺激素细胞, 也可以特异性刺激 GnRH 介导的 LH 分泌, 通过刺激 GnRH 释放到垂体门静脉血液中, 增强促性腺激素的分泌^[16,65]。研究发现, 表达 GALP 神经元中的 PI3K 信号以性别特异性的方式调节下丘脑 GALP mRNA 表达和 LH 水平, 这种现象表现在雌性小鼠上^[66]。

2.2.2 初情期和性行为调控

GALP 在青春期启动过程中也发挥着重要作用, 虽然 GALP 没有显著改变青春期开始的时间, 但敲除 GALP 基因的大鼠显示出青春期启动显著延迟的现象, 这种延迟效果在雌性中出现^[67]。

GALP 对性行为的调控存在明显的性别差异: 在雄性中, 中枢 GALP 的阻断会导致正常成年大鼠性行为的丧失, 而在性腺完整和阉割的雄性大鼠中, 静脉注射 GALP 能刺激雄性的性行为; 在雌性中, GALP 可轻微减少雌性小鼠脊柱前凸行为的发生, 并且显著延长小鼠接受性的潜伏期^[68-69]。

2.2.3 代谢-生殖平衡

GALP 作为下丘脑分泌的关键神经肽, 是连接代谢稳态与生殖功能的核心信号分子。GALP 是瘦素介导的能量平衡调节通路的重要下游效应因子, 瘦素由脂肪细胞分泌, 可通过血脑屏障作用于下丘脑的瘦素受体阳性神经元, 而 GALP 神经元内高表达瘦素受

体, 即瘦素可以刺激 GALP 的释放^[63,70-71]。当机体能量充足 (脂肪储备增加) 时, 瘦素水平升高, 激活 GALP 神经元, 促进 GALP 分泌, 进而激活 HPG 轴; 当能量缺乏 (饥饿或肥胖导致瘦素抵抗) 时, 瘦素信号减弱, GALP 表达下降, HPG 轴活性被抑制^[65]。在瘦素缺乏型肥胖小鼠中, 与野生型小鼠相比, GALP mRNA 表达量减少了 70%, 外源补充瘦素可恢复 GALP mRNA 表达的细胞数量^[72]。这种代谢-生殖整合作用在糖尿病模型中同样显著。1 型糖尿病大鼠交配行为与对照组相比显著减少, 且不会出现射精行为, 外源注射 GALP 可以恢复其性行为能力, 这提示 GALP 在代谢性生殖障碍中具有潜在的治疗价值^[68,73]。

2.3 SPX 是生殖功能的“负向调控者”

SPX 几乎存在于所有物种的大脑中, 特别在中枢神经系统中下丘脑中表达量最高^[74-75]。性腺和外周生殖系统中同样见 SPX 的免疫反应, 卵巢颗粒细胞、黄体细胞和间质细胞等均有表达^[23,76]。SPX 与 GAL、GALP 的作用似乎相反, 以抑制生殖功能为核心, 其调控作用涵盖中枢 HPG 轴和外周性腺两个层面, 在非哺乳动物中作用更显著^[77-78]。

2.3.1 中枢层面对激素的抑制作用

中枢层面, SPX 以“下丘脑-垂体”为核心调控 HPG 轴上游信号。在下丘脑, SPX 主要通过调控 GnRH 神经元活性发挥作用。在扬州鹅长光周期的繁殖模型中, 长时间的光照下调了下丘脑中 SPX 的表达, 同时 GnRH 表达水平显著升高, 证实下丘脑 SPX 与 GnRH 的负向调控关系, 明确光周期通过调控 SPX 的表达影响季节性繁殖^[79]。对石斑鱼和金鱼的研究发现, 在卵巢发育过程中以及繁殖季节, 下丘脑中 SPX 的表达量下调, 这进一步证明了 SPX 在生殖功能上的负向调节作用^[80-81]。

在垂体层面, 鱼类研究最为明确: 在金鱼中腹腔注射 SPX 可有效抑制血清 LH 水平, SPX 能显著抑制培养的金鱼垂体细胞中 LH 的释放; 在罗非鱼试验中, 腹腔注射 SPX (10 $\mu\text{g/kg}$) 可使血浆 LH 和卵泡刺激素 (FSH) 水平均显著降低, 垂体切片培养试验证实其可直接作用于促性腺激素细胞^[81-82]。值得注意的是, 哺乳动物中枢调控存在物种差异: 在大鼠脑室注射 SPX 使得 GnRH mRNA 表达量提高 1.56 倍, 血清中 LH、FSH、T 均显著提高, 因此 SPX 对生殖功能的调控可能具有物种差异性^[83]。

2.3.2 外周层面对性腺发育的调控作用

外周层面, SPX 直接作用于性腺组织并参与生殖疾病调控。在雌性生殖系统中, 人类卵巢颗粒细胞高表达 SPX 及其受体, SPX 可以通过降低 E_2 的合成,

导致颗粒细胞增殖减少，从而影响卵巢功能^[23]。

3 展望

GAL、GALP 与 SPX 通过“中枢调控 HPG 轴+外周作用生殖器官”的双重通路，形成生殖调控网络，其核心功能是整合能量代谢信号与生殖需求，确保生殖功能的有序进行与机体的能量平衡：GALP 作为“代谢-生殖桥梁”，在能量充足时激活生殖；GAL 作为“信号增强者与执行者”，放大生殖信号并推动胎儿排出以及母性行为的发生；SPX 作为“负向调控者”，在能量不足或应激状态下抑制生殖，保存能量。

然而 GAL、GALP 与 SPX 的确切作用机制仍有待充分阐明，可能是通过选择性地结合 GALR 以调节各种生物功能和相关疾病状况。三者与 kisspeptin、GnRH 等核心生殖因子的具体交互机制尚未完全阐明，构建完整的生殖调控信号网络是未来的研究重点。深入解析 GAL、GALP 与 SPX 的畜禽生殖调控机制，其应用前景直接指向养殖生产痛点。基于三者研发的靶向制剂，可实现多重养殖价值：针对能量失衡导致的繁殖障碍（如高产奶牛产后能量负平衡引发的排卵延迟、母猪限位饲养导致的乏情），研发 GALP 作为激动剂以“解锁”生殖抑制状态；针对产程过长问题，研发 GAL 调控制剂优化子宫收缩节律，降低母猪死胎率与助产成本；针对应激性繁殖抑制，开发 SPX 拮抗剂以缓解运输、转群等应激对繁殖性能的冲击。未来，神经肽调控技术与营养调控、环境优化等养殖技术的融合，将为提升畜禽繁殖健康、推动高效生态养殖提供核心支撑。

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