

胰岛素样肽在生理状态及疾病中的作用研究进展

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摘要

胰岛素样肽(Insulin-like Peptide, INSL)是一类进化保守、功能多样的小分子信号肽, 主要功能是调控代谢和生长发育, 其异常表达与隐睾症、妊娠相关疾病、糖尿病、肺癌、乳腺癌等多种疾病有关。INSL是一种多效能的激素, 在生殖系统发挥重要的作用, 此外, 还在胃肠道、下丘脑、胰腺等组织器官参与复杂的病理生理调节。本文综述了INSL在生理状态及疾病中生物学功能的研究进展。

关键词

胰岛素样肽, 松弛素家族肽受体, 生殖, 代谢调控

Research Advances on the Role of Insulin-Like Peptides in Physiological States and Diseases

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Abstract

Insulin-like Peptides (INSLs) are a class of evolutionarily conserved, functionally diverse small signaling peptides. Primarily involved in regulating metabolism and growth, their aberrant expression

has been associated with various pathologies including cryptorchidism, pregnancy-related disorders, diabetes, lung cancer, and breast cancer, among others. As pleiotropic hormones, INSLs play crucial roles in the reproductive system, while also participating in complex pathophysiological regulation within the gastrointestinal tract, hypothalamus, pancreas, and other organs. This review summarizes recent advances in understanding the biological functions of INSLs under both physiological conditions and disease states.

Keywords

Insulin-Like Peptides, Relaxin Family Peptide Receptors, Reproduction, Metabolic Regulation

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1. 引言

胰岛素家族由胰岛素、胰岛素样肽(INSL3, INSL4, INSL5, INSL6)、胰岛素样生长因子 I 和 II (IGF I 和 IGF II)以及松弛素(relaxin-1, relaxin-2, relaxin-3)组成。其中胰岛素和胰岛素样生长因子与酪氨酸激酶受体结合,而松弛素/胰岛素样肽家族的大多数成员被认为作用于 G 蛋白偶联受体。INSL 与胰岛素在序列和结构上有一定的相似性,所有成员均含有保守的胰岛素样结构域,通过特定的二硫键模式维持其三维结构。INSL 通过与特异性受体结合,调控生殖系统的发育、代谢与能量平衡等生理过程,同时在心血管系统、神经系统、免疫调节等方面发挥重要的作用。本文就 INSL 在生理状态及疾病中生物学功能进行综述。

2. INSL3 及其受体的分布及功能

20 世纪 80 年代,在研究睾丸和卵巢功能时,研究人员发现了一些与胰岛素结构相似的肽类激素,并将这一家族命名为胰岛素样肽。其中 INSL3 主要在睾丸间质细胞和卵巢卵泡膜细胞合成,可通过内分泌、自分泌和旁分泌的方式发挥作用。松弛素家族肽受体 2 (RXFP2)是在睾丸、引带、卵巢、肾、脑、肌肉、骨、甲状腺和肾上腺中表达的 A 类 G 蛋白偶联受体(GPCR),而且 RXFP2 是 INSL3 和 relaxin-2 的高亲和力受体。INSL3 与 RXFP2 结合后,在睾丸下降、男性生殖系统发育、女性卵巢功能及生殖激素调节中起关键作用,对生殖健康有重要影响。

2.1. INSL3 在男性生殖中的作用

INSL3 是功能成熟、完全分化的睾丸间质细胞的生物标志物。在胎儿阶段,INSL3 由睾丸间质细胞群产生,促进睾丸的下降;在 2~4 个月的婴儿期,循环 INSL3 小幅升高,之后在儿童期无法检测到 INSL3。直到约 9~11 岁的青春发育期,随着睾丸间质细胞的不断成熟,血液中 INSL3 的含量逐渐增加,在 18~24 岁左右的年轻男性中达到最大值[1]。成年后,INSL3 随年龄的增长而下降,是性腺功能减退的标志[2]。睾丸间质细胞功能明显受损时,睾酮、雄烯二酮和 INSL3 分泌减少。与对促黄体生成素(LH)刺激敏感的睾酮不同,INSL3 水平长期受下丘脑-垂体-性腺轴的调节,波动幅度更小。而且 INSL3 直接依赖于睾丸间质细胞的数量和分化状态,所以它是反映睾丸间质细胞功能的理想标志物。

隐睾症,是新生儿中最常见的先天性疾病(出生时高达 3%~4%) [3]。研究显示,在 INSL3 或 RXFP2 的双等位基因破坏的小鼠中具有隐睾症的表型,出现睾丸经腹下降期的失败[4]。除了在胚胎发育过程中

睾丸下降中的作用外,一些动物模型也显示 INSL3 和 RXFP2 参与了出生后精子的形成。

INSL3 的动物体内治疗可显著减轻了促性腺激素释放激素(GnRH)拮抗剂诱导的睾丸重量下降和生殖细胞的凋亡[5]。而 INSL3 的降低则会导致促凋亡基因 CASP3 和 BAX 表达增加,抗凋亡基因 XIAP 和 BCL2 表达减少以及生殖细胞的凋亡增加,最终表现为睾丸重量下降和精子产量的减少[6],这些动物模型研究均支持 INSL3 及其受体 RXFP2 在精子发生中的作用。但也有相反的结论指出,小鼠 RXFP2 的条件性失活不影响精子的发生和生殖细胞的凋亡[7],这可能表明小鼠中存在遗传冗余。由于锌是 5 α -还原酶合成所必须的,后者促使睾酮转化为二氢睾酮,因此补锌组大鼠血清 INSL3 水平高于缺锌组[8],这表明在精子的发生过程中,补锌饮食在 INSL3 的变化中起着重要作用。

2.2. INSL3 在女性生殖中的作用

除睾丸间质细胞以外,INSL3 还由中型和大型窦状卵泡以及黄体中的卵泡膜细胞产生,并与窦卵泡计数(AFC)呈正相关[9],而卵巢早衰(POI)的女性血清和卵泡液中 INSL3 缺乏[10]。有研究显示,INSL3 在羊水水中的浓度与出生体重增加、先兆子痫发生率和产妇高龄呈正相关[11]。此外,由于雄烯二酮是窦卵泡颗粒细胞产生雌激素的主要类固醇前体,而雄烯二酮合成又依赖于 INSL3,因此 INSL3 敲除小鼠可出现卵泡、排卵和产仔数量减少,以及部分小鼠的不孕[12]。

2.3. INSL3 在其他疾病中的作用

在代谢类疾病中,INSL3 的减少与男性生育力的降低具有相关性。例如在 1 型糖尿病(T1D)的发病过程中通常出现氧化应激的增加和下丘脑-垂体-性腺轴的损害,这导致睾丸间质细胞的活性以及产生 INSL3 的能力降低,从而改变了精子的形成和降低了精子质量[13]。INSL3 也可通过增加人肾上腺细胞中类固醇激素的分泌使血压升高[14],又因为存在下丘脑-垂体-肾上腺轴的负反馈机制,所以库欣病患者的血清 INSL3 水平显著降低[15]。此外,INSL3 的抗炎作用虽不如泼尼松龙显著,但其对巨噬细胞活力和形态学的影响更有利,在多种自身免疫疾病的治疗中与常规疗法联合应用,可减少糖皮质激素治疗引起的副作用[16]。也有研究发现,INSL3 对骨与骨骼肌代谢和功能具有调节作用,低水平的 INSL3 与肌肉减少症和骨质疏松症密切相关[17]。

3. INSL4 的分布及功能

INSL4 基因定位于染色体 9 p24,由 2 个外显子和 1 个内含子组成。其分布具有组织和细胞特异性,主要由合体滋养层和母体蜕膜产生[18]。INSL4 在子宫中表达量较少,而在胎盘中高度表达,尤其是妊娠早期和中期的胎盘,对胎盘的发育和功能维持具有重要作用[19],但其靶受体尚未确定。INSL4 基因编码的早期胎盘胰岛素样肽(EPIL)存在于妊娠期的胎盘中,在妊娠早期参与维持子宫内膜蜕膜化[20],在妊娠中发挥重要的作用。在胎盘中,INSL4_mRNA 在分化的合体滋养层细胞中的表达比在细胞滋养层细胞中更强,而 EPIL 的前体(pro-EPIL)在细胞滋养层细胞中的表达则高于合体滋养层细胞[21]。

3.1. INSL4 在妊娠中的作用

INSL4 的主要生理学功能是参与胎盘的发育和功能维持。在自然分娩前后,胎盘周围、基底膜、滋养层与绒毛膜的 INSL4 表达显著增加。研究表明,INSL4 可引起细胞凋亡,虽然胎盘细胞凋亡是胎盘正常发育所需要的,然而过度的凋亡则有可能导致胎儿生长受限[19]。在胚胎组织中,四肢、椎骨、肋骨的软骨膜及骨间韧带中均有 INSL4_mRNA 的表达[18],这表明 INSL4 可能在滋养层发育和骨形成的调控中发挥重要作用。

3.2. INSL4 在癌症中的作用

除了在胎盘组织中的表达和作用, INSL4 也可表达于多种肿瘤组织和细胞中, 并在肿瘤的侵袭和转移中发挥作用。有研究通过体外选择, 在高侵袭力的乳腺癌细胞亚克隆中检测到 INSL4 的上调[22], 而 INSL4 的升高也同样促进了乳腺癌细胞的侵袭性[23]。在非小细胞肺癌(NSCLC)中, 抑癌基因 LKB1 的缺失会促使 INSL4 水平的急剧升高, 并通过自分泌的方式激活 PI3K-AKT 与 MAPK 途径, 促进肿瘤细胞的生长和活性[24]。DNA 甲基转移酶抑制剂可增强 INSL4 的表达, 这一结果与超过 50% 的甲状腺髓样肿瘤中 INSL4 基因启动子低甲基化的发现相一致[25], 因此启动子去甲基化可能是肿瘤中 INSL4 激活的机制。

4. INSL5 及其受体的分布及功能

INSL5 是一种促食欲的肠道激素, 主要存在于结肠和直肠内分泌 L 细胞中[26], 通过肠神经系统发挥作用[27]。腹膜内给予 INSL5 可剂量依赖性地增加小鼠的摄食量, 表明该胰岛素样肽可能通过作用于外周靶点而非中枢神经系统发挥其促食欲的作用[28]。INSL5 是松弛素家族肽受体 4 (RXFP4) 的同源配体, 可高效激活 RXFP4, 但不激活 RXFP1 或 RXFP2, 并且是 RXFP3 的弱拮抗剂[29]。人类单细胞 RNA 序列数据(scRNASeq)显示, RXFP4 主要存在于产生 5-羟色胺(5-HT)的肠道嗜铬细胞亚群中[30], 此外, 在心脏、胎盘、骨骼肌和胰腺中也可检测到 RXFP4 的存在[31] [32]。

4.1. 调节葡萄糖稳态

INSL5 在调节葡萄糖稳态方面发挥着重要的作用。动物实验显示, INSL5 可增加 MIN6 胰腺 β 细胞的胰岛素分泌和小鼠肠内分泌 GLUTag 细胞的胰高血糖素样肽 1 (GLP-1) 的释放, INSL5 与其受体 RXFP4 的相互作用可能构成了参与代谢和能量平衡调节的肠促胰岛素系统[33]。INSL5 基因敲除小鼠的平均胰岛面积和胰腺 β 细胞数量减少, 从而导致胰岛素生成减少和血糖水平升高, 最终引发葡萄糖稳态功能障碍, 而 INSL5 的急性全身给药可改善小鼠的葡萄糖耐量[34]。人胰腺组织中的 RXFP4 高表达, 但 INSL5 在胰岛中不表达, 这表明 INSL5 可能通过内分泌的方式对葡萄糖进行调节。

4.2. INSL5 在疾病中的作用

研究显示, 肥胖患者通过腹腔镜行袖状胃切除术减轻体重后, 其血浆 INSL5 显著低于术前水平。由于脂肪组织不表达 INSL5, 因此其水平的降低不是直接由脂肪组织的损失所导致的[35], 可能与睾酮循环水平的恢复有关。

来自于生殖系统的研究表明, INSL5 可通过与定位于人类精子的颈部和中段的 RXFP4 结合, 减少精子线粒体活性氧(ROS)的生成, 使其整体活力得到保护[36], 而 INSL5 基因敲除的雄性小鼠由于精子活力显著降低表现出生育能力的下降[34]。在多囊卵巢综合征(PCOS)的患者血液中 INSL5 水平升高, 这可能与雄激素分泌增加和慢性无排卵有关[37]。

在鼻咽癌中, INSL5 可增强 STAT5 的磷酸化和核转位, 促进糖酵解基因的表达, 导致肿瘤细胞糖酵解水平的提高。用 2-脱氧-D-葡萄糖(2-DG)抑制糖酵解或用中和抗体阻断 INSL5, 可逆转 INSL5 诱导的细胞增殖和侵袭, 这提示 INSL5 有可能成为鼻咽癌治疗的潜在靶点[38]。在结直肠癌中, INSL5 在肿瘤组织中的表达低于正常组织, 其低表达与结直肠癌的不良预后密切相关, 而 INSL5 的过表达可显著抑制肠癌细胞的增殖, 并促进聚腺苷二磷酸核糖聚合酶(PARP)的剪切[39]。

5. INSL6 的分布

INSL6 基因定位于染色体 9p24, 靠近 INSL4 和常染色体睾丸决定因子基因座。INSL6 在睾丸组织中

高表达,尤其是特异性地表达于精母细胞和圆形精子细胞中。此外,INSL6也可少量表达于肾脏、胎盘、前列腺和唾液腺中[40]。

5.1. INSL6 在肌组织中的作用

INSL6 在心脏毒素(CTX)的损伤或 AKT 信号的诱导后而上调,促进肌肉祖细胞的存活和增殖[41],在血管紧张素 II 和异丙肾上腺素诱导的心脏应激模型中,内源性 INSL6 蛋白减轻了心脏收缩功能障碍和心脏纤维化,可用于心力衰竭的治疗[42]。在自身免疫性肌炎模型中,INSL6 缺陷小鼠显示出了更严重的运动功能损伤,而 INSL6 过表达则可使损伤减轻。

5.2. INSL6 其他方面的作用

尽管 INSL6 在男性生殖细胞中呈高水平表达,但是缺乏 INSL6 的雄性和雌性小鼠表型仅部分具有不育性,这可能与 INSL6 功能中存在一定程度的冗余,保留了与其他基因重叠的一些功能有关[43]。此外,INSL6 可与跨膜蛋白 MAEA 相互作用并可促进巨噬细胞的成熟[44]。

6. 总结

胰岛素样肽家族成员通过多受体、多通路机制,在代谢调控、生殖与发育、抗凋亡、细胞增殖与分化以及肿瘤的演进等方面发挥着核心作用。生理水平维持机体稳态,但失衡可能导致代谢性疾病、肿瘤等的发生。未来关于胰岛素样肽家族成员的研究需聚焦于组织特异性调控和精准干预策略的开发。

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