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· 综述 ·

糖皮质激素性骨质疏松症的药物作用机制研究进展

李昊然[1] 高璐[2*] 迟湘胤[1] 张东方[2] 侯赫[1]
1. 中国医科大学药学院,辽宁 沈阳 110122
2. 中国医科大学药学院中药与生药学教研室,辽宁 沈阳 110122

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摘要: 糖皮质激素是常见的抗炎药物,长期使用会导致骨质疏松症,增加骨折发生率,严重影响患者的生活质量。相关药物通过调控 Wnt/β-catenin、OPG/RANK/RANKL 和 BMP/Smad、AKT、ERK 等信号通路中基因与蛋白的表达,影响成骨细胞与破骨细胞增殖分化,调节骨形成与骨吸收过程,发挥治疗糖皮质激素性骨质疏松的作用。本文对糖皮质激素性骨质疏松的发病机制与药物作用机制进行概述。西药包括临床常用的维生素 D 与钙剂、双膦酸盐、甲状旁腺素和狄诺塞麦等。中药包括淫羊藿、熟地黄、栀子、巴戟天和龟板等。

关键词: 糖皮质激素性骨质疏松症;发病机制;药物作用机制

Advances in the mechanism of drug action in the glucocorticoid osteoporosis

LI Haoran[1], GAO Lu[2*], CHI Xiangyin[1], ZHANG Dongfang[2], HOU He[1]
1.School of Pharmacy, China Medical University, Shenyang 110122
2.Department of Traditional Chinese Medicine And Pharmacognosy, China Medical University, Shenyang 110122, China
* Corresponding author: GAO Lu, Email: 277418326@qq.com

Abstract: Glucocorticoid is a common anti-inflammatory drug. Long-term use of glucocorticoid leads to osteoporosis, increases the incidence of fracture, and seriously affects the quality of life of patients. By regulating the expression of genes and proteins in Wnt/β-catenin, OPG/RANK/RANKL, BMP/Smad, AKT, ERK and other signaling pathways, the drugs can affect the proliferation and differentiation of osteoblasts and osteoclasts, regulate the process of bone formation and bone absorption, and play a role in the treatment of GIOP. In this paper, the pathogenesis and drug action mechanism of glucocorticoid-induced osteoporosis are summarized. Western drugs include vitamin D and calcium, bisphosphonates, parathyroid hormone and Denosumab which are commonly used in the clinic. Chinese herbs include Icariin, Rehmanniae Radix Preparata, Geniposide, Morinda officinalis and Plastrum testudinis.

Key words: glucocorticoid-induced osteoporosis; pathogenesis; pharmacological mechanism

骨质疏松症(osteoporosis, OP)是最常见的骨骼疾病。OP 患者的骨量减少、骨微结构损坏、骨脆性增加,易发生骨折[1]。糖皮质激素(glucocorticoid, GC)具有显著的抗炎和免疫抑制作用,常用于自身免疫性疾病、支气管哮喘等疾病的治疗[2]。长期使用 GC 易导致糖皮质激素性骨质疏松症(glucocorticoid-induced osteoporosis, GIOP)[3]。本文拟对 GIOP 发病机制与药物作用机制进行综述,为临床治疗与药物开发提供更多思路。

1 GIOP 的发病机制

骨的稳态依靠骨形成和骨吸收共同调节,成骨细胞(osteoblast, OB)参与骨形成,破骨细胞(osteoclast, OC)参与骨吸收。当骨吸收大于骨形成时,出现骨量丢失。

Wnt/β-catenin 信号通路与骨形成有关[4],Wnt 与细胞膜上的受体卷曲蛋白(sFrps)结合后,糖原合成酶激酶 3β(GSK3β)发生磷酸化,进而 β-catenin 进入细胞核,促进淋巴增强因子基因转录,维持正常的骨形成。Wnt 拮抗剂 DKK-1 可与细胞膜另一受体低密度脂蛋白受体相关蛋白(LRP5/6)相结合,扰

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* 通信作者: 高璐,Email:277418326@qq.com

乱 GSK3β 的磷酸化,使得 β-catenin 磷酸化,磷酸化后的 β-catenin 则不能进入到细胞核中调控基因的转录[5]。GC 提高 DKK1 和硬化蛋白的表达,激活 GSK3β,使 β-catenin 失去稳定性,进而抑制 OB 的分化[6-7]。GC 也会抑制分化型胚胎软骨发育基因 1(DEC1)的表达,DEC1 可以通过调节 β-catenin 的表达,调节 Wnt/β-catenin 信号通路,促进成骨。DEC1 表达增多,成骨活动增加,DEC1 的表达减少时,抑制充质干细胞(MSC)向 OB 分化[8-9]。

OPG/RANK/RANKL 信号通路是调节骨代谢的重要通路[10]。RANKL 与 OB 上的受体 RANK 结合后抑制 OB 增殖分化,促进 OC 分化成熟并抑制其凋亡,促进骨吸收。骨保护素(osteoprotegerin,OPG)阻断 RANKL 和 RANK 结合,抑制破骨细胞骨吸收[11]。GC 会下调 OPG,上调 RANKL 的 mRNA 和蛋白表达,促进破骨细胞骨吸收[12]。

Notch 信号通路在 OB 和 OC 的分化以及骨骼发育、重塑中起着关键作用。成骨细胞前体细胞中缺失 Notch1 和 Notch2 受体时,成骨细胞数量增加、骨形成增多、骨体积增加。GC 会增强 Notch1 和 Notch2 受体的转录,导致 GIOP[13]。

GC 可影响钙吸收,钙通过离子通道进入肠黏膜上皮细胞,进入细胞的钙与钙结合蛋白结合后在胞内转运,最后经过基底膜侧的钙泵,完成肠道对钙的吸收。GC 抑制肠粘膜上皮细胞上的细胞离子通道蛋白 TRPV6 和钙结合蛋白 CaBP-9k 的表达,减少钙进入肠粘膜上皮细胞,并抑制钙与钙结合蛋白结合后在胞质内的转运,进而减少肠道对钙的吸收[14]。

GC 可减少胰岛素样生长因子(IGF-1)的合成,IGF-1 可调节骨代谢,促进骨胶原形成,增加成骨细胞的数量,增强 OB 的活性,减少或限制 OC 的分化[15]。过量 GC 可以使 IGF-1 合成减少,减少骨形成,并诱导 OC 分化,进而诱发 GIOP[16]。

2 GIOP 的药物作用机制

预防和治疗轻度 GIOP 时,可使用维生素 D 和钙剂联用,增加骨密度(bone mineral density,BMD),降低骨折风险等[17-18]。治疗中重度 GIOP 时,首选双膦酸盐。阿仑膦酸钠可以提高 GIOP 患者的腰椎和股骨 BMD,减少骨质流失。如联用维生素 D 和钙剂,疗效更为显著[19-20]。如患者不能耐受阿仑膦酸钠,则可选用二线药物如甲状旁腺素、狄诺塞麦等[21]。

2.1 维生素 D 和钙剂

维生素 D 在肝和肾的作用下代谢为 1,25(OH)$_2$D$_3$,可促进钙结合蛋白生成,增强钙泵的作用,促进钙的吸收。研究[22]显示,局部肾素-血管紧张素(RAS)的激活具有促进 OC 增殖分化的作用,1,25(OH)$_2$D$_3$ 可下调 GIOP 模型鼠的 RANKL 和 RAS 系统中血管紧张素Ⅱ的受体 AT2R 基因的表达,抑制 RAS 系统的激活,进而抑制 OC 增殖分化,抑制骨吸收,发挥治疗 GIOP 作用。

2.2 双膦酸盐

双膦酸盐可与骨表面的羟磷灰石强有力地结合,双膦酸盐不易被水解,可沉积在骨组织内被 OC 摄取,抑制 OC 的活性并诱导其凋亡,进而抑制骨吸收[23]。双膦酸盐下调 RANKL 的表达,抑制 OC 增殖分化[24]。此外,双膦酸盐还可下调骨形态发生蛋白(BMP)拮抗剂和 Wnt 拮抗剂表达,调节 BMP/Smad 和 Wnt/β-catenin 信号通路,抑制骨吸收,促进骨形成,治疗 GIOP[23]。

2.3 甲状旁腺素

甲状旁腺素(PTH)是甲状旁腺释放的钙调节激素,可以在腺苷酸环化酶(cAMP)的介导下,降低血磷、升高血钙,促进骨转换。GC 会增加小鼠骨细胞内的活性氧(ROS)水平,特立帕肽(PTH 的活性片段)可通过降低 ROS 水平,激活丝苏氨酸蛋白激酶(AKT)通路,促进丝苏氨酸蛋白激酶(AKT)表达,AKT 通过调节下游靶蛋白的磷酸化,促进骨细胞增殖,活化的 AKT 可以抑制促进骨吸收的蛋白水解酶半胱氨酸天冬氨酸蛋白酶 caspase-3 的活性,抑制骨细胞中凋亡级联反应,促进骨细胞增殖[25]。

2.4 狄诺塞麦

狄诺塞麦是 RANKL 单克隆抗体,与 RANKL 具有较高的亲和力,狄诺塞麦与 RANKL 结合后,阻断了 RANKL 与其受体 RANK 的结合,减少 OC 的数量[26]。狄诺塞麦通过作用于 OPG/RANK/RANKL 这一细胞通路,发挥治疗 GIOP 的作用。

2.5 中药

2.5.1 中药提取物及其活性成分:①淫羊藿提取物淫羊藿苷可以抑制 OB 凋亡,减轻 GC 引起的钙代谢紊乱和骨吸收失衡程度,增加血清碱性磷酸酶(ALP)、减少促进骨吸收的羧基末端胶原蛋白,维持骨的正常矿化速度,刺激小鼠的骨重建[27-28]。OC 释放的组织蛋白酶 K(CTSK)在骨重塑的过程中参与降解骨基质,促进骨吸收。淫羊藿苷通过增加 miRNA-186 的表达,下调 CTSK 的表达,从而发挥保

护骨骼的作用[29]。此外,淫羊藿苷可与 RUNT 相关转录因子 2(RUNX2)受体结合,促进 MSC 向 OB 分化,促进骨形成[30];②熟地黄提取物会上调 RUNX2 和骨桥蛋白(osteopotin,OPN)表达,增强 ALP 的活性,提高成骨活性,促进细胞外基质矿化,提高 BMD,改善骨微结构。代谢组学分析显示:熟地黄提取物通过上调甾体激素合成过程中的关键蛋白细胞色素 P450 17A1 和芳香化酶 CYP19A1 表达,下调 11β-羟类固醇脱氢酶 HSD11B1 表达,提高雌激素水平,预防 GIOP[31];③栀子中提取物栀子苷会提高 ALP 的活性,促进骨形成。栀子苷也可以促进小鼠成骨细胞前体细胞 MC3T3-E1 细胞向 OB 分化。使用 GC 处理 MC3T3-E1 细胞后,OPN、RUNX2、成骨相关转录因子(OSX)等表达下调,治疗组中均有上调。提示栀子苷可通过提高 RUNX2 和 OSX 等转录因子表达,增强成骨活动。有研究[32]指出栀子苷是胰高血糖素样肽 1(GLP-1)受体激动剂,栀子苷可以通过 GLP-1 受体激活细胞外信号调节激酶(ERK)通路,ERK 磷酸化后激活 RUNX2,从而促进 OB 增殖分化,治疗 GIOP;④巴戟天及其主要成分水晶兰苷和甲基异茜草素可促进 OB 增殖,提高 ALP 的活性,增强其矿化能力。巴戟天下调脂氧合酶(5-LOX)、白三烯 A4 水解酶(LTA4H)等代谢酶的表达,干扰花生四烯酸的代谢,促进 MSC 向 OB 分化,促进骨形成,减少骨量丢失[33];⑤龟板提取物(PTE)可增加 BMD 和骨矿物含量(BMC),改善骨微结构,增强骨强度。PTE 可通过上调 OPG 的表达,抑制破骨细胞骨吸收来发挥治疗 GIOP 的作用[34]。还可通过调节丝裂原激活蛋白激酶 MAPK 通路中的 p38MAPK 及其相关基因和蛋白表达,上调 STE20 样激酶(STE20)、IGF-1 受体、p38MAPK 蛋白表达,下调肿瘤坏死因子受体相关因子 6(TRAF6)蛋白表达,进而促进骨髓间充质干细胞(BMSC)的分化成熟,促进骨形成、增加骨骼矿化、维持骨量[35];⑥川续断的主要活性成分木通皂苷 D 通过激活 BMP/Smad 信号通路,上调成骨相关因子 RUNX2、BGP、Smad1 和 Smad5 的 mRNA 表达,磷酸化的 Smad1、Smad5 和 Smad8 形成复合物后与 Smad4 结合,进入细胞核与转录因子 RUNX2 作用,促进 BMSC 向 OB 分化,治疗 GIOP[36];⑦菟丝子提取物增加 IGF-1 和转化生长因子(TGF-β)等生长因子的表达,TGF-β 增强 I 型胶原蛋白的表达,促进骨形成,IGF-1 调节 β-catenin 的稳定性,促进骨形成。菟丝子提取物会上调 OPG、下调 RANKL 基因和蛋白的表达,通过 OPG/RANK/RANKL 信号通路,治疗 GIOP[12];⑧川芎的活性成分川芎嗪通过 AMPK/mTOR 途径,促进 AMPK 磷酸化,抑制 mTOR 磷酸化,进而促进 BMSC 自噬,保护 BMSC,提高 GIOP 小鼠的 BMD[37]。

2.5.2 中成药:①左归丸可提高 GIOP 模型鼠 BMD,增加骨小梁数量,显著下调 DKK1 mRNA 表达,通过 Wnt/β-catenin 信号通路促进 OB 增殖分化进而治疗 GIOP[38];②复方贞术调脂胶囊由女贞子、白术、丹参、佛手、杜仲组成,可提高 β-catenin 转录活性,上调 β-catenin 和促分裂原活化蛋白激酶激酶激酶 2(MEKK2)蛋白表达,MEKK2 可有效维持 β-catenin 的稳定,抑制 MSC 向脂肪细胞分化,稳定成骨细胞,治疗 GIOP[39]。

3 小结

一些药物如双膦酸盐、菟丝子、左归丸和复方贞术调脂胶囊等通过 Wnt/β-catenin 信号通路治疗 GIOP;川续断通过 BMP/Smad 信号通路治疗 GIOP;淫羊藿、熟地黄、栀子和川续断等会通过影响 RUNX2 调控基因转录,影响 OB 增殖分化。一些药物也会通过影响糖类、脂质、花生四烯酸的代谢,治疗 GIOP,但通路并不十分清晰。治疗 GIOP 药物的作用机制是否有更多,仍需要更多深入的研究。

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