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·综述·

帕金森病致骨代谢异常的中枢机制研究进展

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摘要:帕金森病(parkinson's disease,PD)是老年人常见的神经退行性疾病。前期研究表明,PD患者比正常人更容易发生骨折。PD患者骨折风险的增加给家庭和社会带来沉重的负担,因此,阐明PD导致骨代谢异常的机制具有重大意义。近年来研究发现PD患者中枢肾素-血管紧张素系统(renin-angiotensin system,RAS)、下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis,HPA)、交感神经系统(sympathetic nervous system,SNS)在骨代谢调节过程中发挥了重要作用。笔者拟从中枢机制的角度对PD相关的骨代谢异常进行总结与讨论。

关键词:帕金森病;骨代谢;肾素-血管紧张素系统;下丘脑-垂体-肾上腺轴;交感神经系统

Research progress on the central mechanisms involved in the disturbance of bone metabolism associated with Parkinson's disease

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Abstract: Parkinson's disease (PD) is a common neurodegenerative disorder in older people. Previous studies suggested that PD patients had an increased risk of fractures as compared with the age-matched controls. The increase in fracture risk associated with PD imposed a huge burden on families and society, therefore, it is necessary to elucidate the real underlying mechanism involved in the disturbance of bone metabolism in PD. Recently, it was found that the central renin-angiotensin system, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system played vital roles in regulating bone metabolism in PD patients, thus, these central mechanisms were summarized and discussed in this review.

Key words: Parkinson's disease; bone metabolism; renin-angiotensin system; hypothalamic-pituitary-adrenal axis; sympathetic nervous system

帕金森病(parkinson's disease,PD)是一种常见的神经系统退行性疾病。我国65岁以上人群的总患病率为1.7%,并随着年龄的增加而增长,男女之间性别差异不明显[1]。荟萃分析结果[2]表明,PD患者比正常人更容易患上骨质疏松症(OR=1.18,95%CI=1.09~1.27)。同正常组相比,PD患者的脊椎、股骨颈、髋部骨密度降低[3]。一项纳入6个研究、包含69 387名参与者的荟萃分析[4],发现PD患者有着更高的骨折风险(HR=2.66,95%CI=2.10~3.36)。以上临床资料表明,PD患者更易发生骨代谢异常、骨量丢失、骨折风险增加,但具体机制尚不明确。

由于PD患者多为老年人群,骨折发生后会出现各种并发症,如肺部感染、泌尿道感染和褥疮等,导致生活质量下降,死亡率增加,给家庭和社会带来沉重的负担[5]。因此,研究PD致骨代谢异常的具体机制具有重要的科学价值与社会意义。已有资料显示[6],可能有多种因素、机制参与PD导致的骨代谢异常,比如PD治疗药物左旋多巴的过度使用、营养缺乏、肌力下降、体重减轻、运动减少、维生素D

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缺乏等。本文拟从中枢系统调控的角度探讨 PD 引起骨代谢异常的潜在中枢机制。

1 中枢 RAS 与骨代谢异常

1.1 RAS

肾素-血管紧张素系统(renin-angiotensin system,RAS)主要参与血压和体液代谢平衡的调节[7]。肾球旁细胞合成肾素(renin),可以将血液中的血管紧张素原(angiotensinogen,AGT)转化为血管紧张素 I(Ang I),然后在血管紧张素转化酶(ACE)的作用下转化为血管紧张素 II(Ang II)。Ang II 与其 1 型(AT1R)和 2 型受体(AT2R)结合进行下游功能调节,并参与一系列病理生理的进程[7]。

1.2 PD 与中枢 RAS

除了循环系统存在 RAS,中枢系统也存在 RAS 组分。研究发现[8],PD 可以激活中枢 RAS、Ang II 生成增加并作用于 AT1R,增加 NADPH 的氧化活性,刺激黑质中多巴胺能神经元产生大量的活性氧自由基(ROS)。同时,Ang II 可以通过激活黑质中线粒体 ATP 敏感性钾通道导致 ROS 进一步增多[9]。ROS 作为多种炎症信号通路的刺激因子,可以引起炎症反应[10]。小胶质细胞(microglia)的 RAS 被激活后,进一步促进炎症反应的发生[11]。此外,Ang II 可以激活 NF-κB 信号通路,使黑质中的炎症因子增加,进一步破坏多巴胺神经元,导致中枢 RAS 被进一步激活,产生更多的 ROS 和炎症因子[12]。

1.3 中枢 RAS 与骨代谢

通过 PD 动物模型的研究[13]发现,中枢系统的炎症、小胶质细胞的激活等可以引起血脑屏障(blood-brain barrier,BBB)的通透性增强。因此,当中枢 RAS 被激活后,产生过多的 ROS 和炎症因子可能会通过开放的 BBB 引起全身炎性因子浸润,最终导致骨代谢的失衡。研究发现[14],使用 H_2O_2 作用于成骨细胞,细胞内 ROS 产量过多,能抑制成骨分化标记物 ALP、OC 和 Runx2 的表达。曹军军等[15]发现,枸橼酸铁铵可以通过提高 ROS 水平并激活 MAPK 通路诱导成骨细胞凋亡。另外,ROS 也可以参与调节破骨细胞功能。Kim 等[16]发现,过量的 ROS 可以导致破骨细胞数量和活性的增加,但这种作用可以被超氧化物歧化酶[(superoxide dismutase,SOD),一种可以抑制细胞内 ROS 的酶]所抑制。

多种炎症因子能够调节骨代谢。TNF-α 可以直接抑制成骨细胞分化[17],IL-1 可以抑制成骨细胞胶原合成[18],而 IL-6 过度表达与骨密度的减少相关[19]。另外,TNF-α 在调节破骨细胞过程中也发挥着重要作用,其能够通过 NF-κB 和 PI3K/Akt 信号通路促进 RANKL 的分泌进而诱导破骨细胞的形成[20]。因此,ROS 产生过多或炎症反应过度都会影响骨代谢平衡。

2 HPA 轴与骨代谢异常

2.1 HPA 轴

下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis,HPA)是一个由下丘脑、垂体和肾上腺共同组成的复杂生理系统。当机体受到应激时,下丘脑室旁核神经元合成并分泌促肾上腺皮质激素释放激素(corticotropin-releasing hormone,CRH),然后 CRH 可以激活垂体产生促肾上腺皮质激素(adenocorticotropin hormone,ACTH),ACTH 随血液到达肾上腺皮质,合成并释放糖皮质激素(glucocorticoid,GC)。正常人体 HPA 轴存在负反馈调节,过量的 GC 可以负反馈作用于肾上腺和垂体,抑制 ATCH 的释放而使 HPA 轴恢复正常[21]。

2.2 PD 与 HPA 轴

临床研究发现,PD 患者常出现 HPA 轴的紊乱。一项纳入 30 例(PD 组、正常组各 15 例)人群的研究[22]显示,16.7% 的 PD 患者血清中的皮质酮(cortisol)水平显著增加。另一项临床研究[23]表明 PD 患者清晨的 cortisol 水平较正常人更高。使用 MPTP 建立 PD 的动物模型,发现血清中 cortisol 和 ATCH 含量较对照组分别增加了 60% 和 40%[24],而且,PD 动物中枢小胶质细胞 GC 受体的表达增强[25]。以上的临床和实验研究表明,PD 能够引起 HPA 轴兴奋。

2.3 HPA 轴与骨代谢

HPA 轴的失稳态可以引起骨代谢的紊乱。研究发现[26],库欣综合征患者由于产生过多的 cortisol,与正常人相比,其骨密度更低,也更容易发生骨折。临床上初次使用 GC 治疗的病人,每年椎体骨折发生率为 5.1%,而慢性患者每年的椎体骨折发生率为 3.2%[27],说明 HPA 轴的兴奋以及活性物质的增加诱导骨量丢失。实验研究[28]表明,过多的 GC 可以抑制成骨细胞分化,增加成骨细胞凋亡。GC 过多还可以上调成脂分化的相关转录因子如 PPARγ,促进 BMSCs 趋向成脂分化,间接抑制了 BMSCs 的成骨分化[29-30]。此外,GC 还可作用于破

骨细胞,减弱细胞凋亡信号,延长破骨细胞的寿命,从而间接增加破骨细胞的数量与骨吸收活性[31]。GC 也可以刺激成骨细胞分泌 RANKL,减少骨保护素(OPG)的表达,而 RANKL-OPG 比例的失调会增强破骨细胞的生成与活力,促进骨吸收[31]。

3 SNS 与骨代谢异常

3.1 SNS

交感神经系统(sympathetic nervous system, SNS)分布于全身各组织器官,参与调节机体各系统的功能,维持机体内、外环境的相对稳定。SNS 可以分泌肾上腺素(epinephrine, E)和去甲肾上腺素(norepinephrine, NE),并通过组织上的肾上腺素能受体(adrenergic receptor, AR)发挥作用[32]。研究发现[33],骨细胞表面也存在 AR 受体,目前发现的 AR 主要有 5 种亚型(α1、α2、β1、β2、β3)。

3.2 PD 与 SNS

心率变异性(heart rate variability, HRV)是一种可以反映交感神经活动性的非侵入性指标,其参数 SDNN(R-R 间期平均值标准差)与交感神经的兴奋性呈正相关。研究发现[34]PD 患者的 SDNN 较正常人显著降低,说明 SNS 兴奋性受到了抑制。PD 患者脑中 NE 的合成量较正常人显著减少,在脑部某些特殊区域,NE 的合成量只有正常组织的一半[35]。在体外将 PD 模型动物的蓝斑核(蓝斑是脑中合成 NE 的主要部位)破坏后,黑质致密部(SNpc)的多巴胺神经元破坏会加重,通过实验方法增加 NE 的合成后,SNpc 中多巴胺神经元的破坏程度将会减轻[36]。这些研究结果表明,PD 可以抑制 SNS 的兴奋。

3.3 SNS 与骨代谢

SNS 对骨代谢的调控发挥着重要作用。不同亚型的 SNS 受体对骨代谢的影响不尽相同。α1 受体激活后可以促进骨形成,而 β2 受体激活后会抑制骨代谢。一项纳入 16 个队列的荟萃分析[37]结果发现,使用 β 受体阻滞剂可以减少 15% 的骨折风险。体外研究[38-39]发现 β2 受体缺乏的小鼠表现为成骨细胞增多,破骨细胞减少,骨量增加。除 β2 受体以外,α1 受体也参与了骨代谢的调节。一项来自韩国的回顾性研究[40]发现,长期使用 α 受体拮抗剂的药物后,女性患者髋部骨折发生率是未使用者的 2.19 倍 (95%*CI*, 1.74~2.77)。Tanaka 等[41]使用哌唑嗪(α 受体拮抗剂)研究发现,该药可以减少骨形成,而使用 α 受体激动剂可以逆转这种现象,其原因可能是 α 受体激动剂可以调控 CCAAT 增强子结合蛋白 δ(CCAAT/enhancer-binding protein delta, Cebpd)的表达,而 Cebpd 可以促进成骨细胞分化。尽管不同的肾上腺素能受体对骨代谢的影响存在不一致性,但笔者推测 PD 患者骨量降低,其原因有可能是 PD 抑制了 SNS 的兴奋,并主要导致 α1 受体通路被抑制,因此骨量减少,然而这些假说还需要进一步的实验研究加以验证。

4 结语与展望

综上所述,PD 患者易发骨折,而且 PD 导致骨代谢异常的具体机制较为复杂。目前,鲜有文献从中枢机制的角度阐释 PD 诱发骨代谢异常的潜在原因。笔者通过总结分析(图 1),发现 PD 可能通过引起中枢 RAS、HPA 轴、SNS 的紊乱而导致骨代谢异常,引起骨折风险增加。另外,本文也为通过干预中枢 RAS、HPA 轴、SNS 进而研发中枢性骨代谢异常的治疗药物提供了新思路。

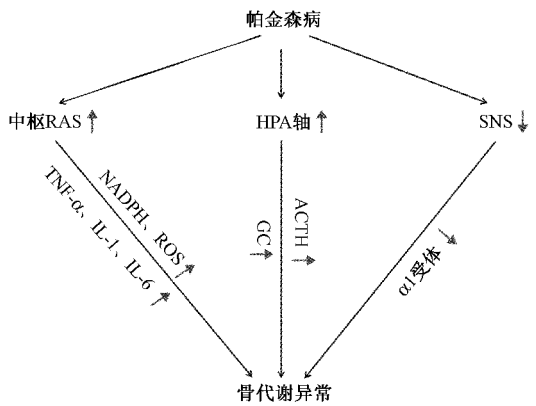

图 1 帕金森病引起骨代谢异常的中枢机制

Fig. 1 Central mechanisms involved in the disturbance of bone metabolism associated with Parkinson's disease

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