中国骨质疏松杂志 2013年7月第19卷第7期 Chin J Osteoporos, July 2013, Vol 19, No. 7
Published online www.wanfangdate.com.cn doi:10.3969/j.issn.1006-7108.2013.07.027

·综述·

酒精性股骨头缺血性坏死与CYP450关系研究进展

李盛华[1] 孙凤歧[2] 周明旺[1*] 郭铁峰[2] 穆欢喜[2]
(1. 甘肃省中医院,兰州 730050; 2. 甘肃中医学院,兰州 730000)

中图分类号: R681 **文献标识码**: A **文章编号**: 1006-7108(2013)07-0773-04

摘要: **目的** 长期过量饮酒引起的股骨头缺血性坏死(osteoarthrosis of femoral head, ONFH)是一种严重威胁人类健康的疾病,多发于20~50岁的青壮年。随着人们生活方式的改变,酒精性股骨头坏死的临床病例日渐增多,酒精性股骨头坏死(alcohol-induced osteoarthrosis of femoral head, AIONFH)的发病机制尚不完全清楚,很多学者认为主要与一些基因有关,各国学者报道情况不一,各持己见;本文就国内外酒精性股骨头坏死与CYP450的关系作一综述。

关键词: 酒精性;股骨头坏死;CYP450;研究进展

Research progress in the relationship between alcohol-induced avascular necrosis of the femoral head and CYP450

LI Shenghua[1], SUN Fengqi[2], ZHOU Mingwang[1], GUO Tiefeng[2], MU Huanxi[2]
(1. Gansu Provincial Hospital of Traditional Chinese Medicine, Lanzhou 730050;
2. Gansu Medical College of Traditional Chinese Medicine, Lanzhou 730000, China)
Corresponding author: ZHOU Mingwang, Email: zmw2006@126.com

Abstract: Osteoarthrosis of the femoral head (ONFH), which is caused by long term over-dose alcohol drinking and happens mostly in young adults at the age of 20 - 50 years old, is a disease that severely threatens human health. Along with the changes of people's lifestyle, clinical cases of alcohol-induced ANFH (AIONFH) increase gradually. The pathogenesis of AIANFH remains unclear. Some scholars consider that this disease is related to some genes, but scholars from different countries have diverse reports and different opinions. This paper reviews the relationship between AIANFH and CYP450 from the national and international studies.

Key words: Alcoholic; Necrosis of the femoral head; CYP450; Research progress

股骨头缺血性坏死(Osteoarthrosis of the Femoral Head, ONFH)是骨科多发病、常见病,多发于20~50岁的青壮年,是一种严重威胁人类健康的骨科疾病[1]。祖国医学典籍中虽无股骨头坏死的病名记载,根据其病理改变、证候特点可归属于祖国医学的"骨痹"、"骨痰"、"骨蚀"范畴。关于骨痹的描述首见于《素问·痹论》:"风寒湿三气杂至,合而为痹也。以冬遇此者为骨痹,以春遇此者为筋痹,五脏皆有合,病久而不去者,内舍于其合也。故骨痹不已,复感于邪,内舍于肾…"。《素问·痿论篇》中载曰:"肾气热而腰脊不举,骨枯而髓减发为骨痿"。《脾胃论》曰:"脾病则下流于肾"……则骨乏无力,是为骨痿,令人骨髓空虚,足不能履也"。《灵枢·刺节真邪》曰:"虚邪之入于身也深,寒与热相搏,久留而内著,寒胜其热,则骨疼而肉枯,热胜其寒,则烂肉腐肌为脓,内伤骨,内伤骨为骨蚀"[2]。因其发病隐匿,病理过程复杂,其确切病因及发病机理尚未完全明了,因此备受国内外学者关注。

1 酒精性股骨头坏死概述

学者们通过长期的临床研究得出了以下几种学说:脂肪代谢紊乱学说、骨内高压学说、骨质疏松学说、激素的细胞毒作用、潜在血管炎、前凝血状态和血管内凝血学说[3,4],大量的临床数据及动物实验表明,在股骨头坏死病程中存在脂质代谢紊乱的现象[5],产生全身性脂肪栓子,栓塞骨内血管最终导致骨坏死,股骨头坏死是一种致残率极高的骨科疾

基金项目: 国家自然科学基金面上项目(81072821/H2710)
* 通讯作者: 周明旺, Email: zmw2006@126.com

病,以骨的活性成分(骨细胞、骨髓造血细胞及脂肪细胞)死亡为主要改变的病理过程。病情进行性加重,如早期不能得到及时有效的治疗,80% 左右的患者会在 1 ~ 4 年内出现股骨头塌陷、关节间隙变窄,导致髋关节功能严重障碍,使病人丧失劳动与生活能力。我国的发病人数已超过 700 万,并且还在逐年上升,有资料表明股骨头坏死已取代了原髋关节结核的位置,居髋关节疾病的首位[6]。文献报道酒精性股骨头坏死在非创伤性股骨头坏死的发病率超过 30% 以上[7],目前还没有一种行之有效的股骨头坏死治疗方法[8]。在现有的非手术治疗方法中,卧床休息、对症止痛、制动患肢、限制承重、高压氧疗法、电磁波刺激疗法、介入治疗及物理疗法等被陆续采用;手术的方法对阻止股骨头蹋陷或股骨头再生,效果均不佳,绝大多数患者仍然不得不采用人工关节置换。但由于股骨头坏死患者大多数为青壮年,人工关节 10 ~ 20 年的使用年限使患者可能需要多次手术,从而给他们的生活和工作带来了无尽的痛苦和负担[9]。因此,深入研究酒精性股骨头坏死的发病机制及其与 CPY450 的相关性有利于揭示酒精性股骨头坏死的诊治和预防。

2 酒精与股骨头坏死的关系

酒精性股骨头坏死的发病机理尚不十分清楚,学术界普遍认为过量饮酒会导致脂质代谢紊乱、高脂血症、髓内压增高、骨细胞脂肪变性和骨质疏松[10-13]。

乙醇的毒性作用使自由基生成增多,导致自由基清除剂超氧化物歧化酶(SOD)活性下降,而自由基具有强烈的引发脂质过氧化作用,损伤血管内皮细胞,使小动脉发生纤维变性和粥样硬化,导致股骨头局部缺血、缺氧发生坏死;过量饮酒使周围循环中脂肪物质增多聚集成脂肪球,使血流滞缓容易栓塞于股骨头内微血管,导致股骨头坏死;而增殖肥大的脂肪细胞可直接压迫血窦,使骨内压升高,微循环淤滞,从而加重股骨头缺血、缺氧;骨细胞功能减退后骨基生成减少,骨小梁变细发生骨质疏松[14]。酒精可能从基因调控水平诱导骨髓基质细胞,使成脂分化增多,成骨分化减少,这可能是发生酒精性骨坏死时骨髓内脂肪堆积而骨修复不足的一个重要原因[15]。以上所有这些因素可加重股骨头缺血、缺氧形成恶性循环,导致股骨头缺血性坏死。

另外,长期大量的摄入酒精导致体内维生素 D 的代谢发生紊乱、性腺机能减退、骨细胞代谢减低、成骨能力减弱,最终导致骨质疏松,负重时股骨头软骨下骨受力面积减少,产生高应力而发生微小塌陷骨折,局部骨内压升高,压迫髓内微血管引起缺血[16]。酒精在人体内可以影响成骨细胞,减少骨钙蛋白的合成与分泌,增加骨钙蛋白的代谢清除率。李骁[17]观察到大量摄人酒精后的试验动物股骨头内骨细胞减少,空骨陷窝增加,骨小梁变细、稀疏,部分发生断裂,面积分数降低。Glueck[18]等研究发现机体在病理状态下内源性前列腺素 E2 分泌增加,血及尿液内皮质醇水平升高,它可促进破骨细胞的吸收,导致骨质疏松发生引起骨坏死。Kawai[19]等发现酒精中毒后可出现类似于夏科氏关节病的病变及圆锥形坏死灶。酒精作用引起骨质疏松以后,导致骨组织不能抵抗压应力,骨的结构遭到破坏,随之出现骨折,骨内压升高诱发骨坏死。

3 酒精性股骨头坏死与 CYP450 的关系

对于酒精性股骨头坏死的患者,同样用量的酒精,有些患者会引起股骨头坏死,有些患者不会引起,说明个体对于高危因素的敏感性是不同的。细胞色素 P450 是参与药物 I 相反应的重要代谢酶,几乎和所有脂溶性药物的代谢过程有关。CYP450 的基因多态性是药物代谢速率存在明显个体差异的主要原因[20]。

细胞色素 P450 酶(cytochromeP450 enzymes, CYPs)是一类含血红素的酶,也称肝药酶,主要存在于肝微粒体中,参与内源性和外源性化合物的生物转化并可活化代谢多种化合物[21-24],定位于人体 7 号染色体长臂 2 区 1 带 3 亚带-22 亚带(q21.3-22)。CYP450 诱导方式分为 5 类:芳香烃受体(arylhydrocarbon receptor, AhR)介导型、乙醇型、过氧化物酶体增殖剂激活受体-γ(Peroxisome Proliferator-activated receptor-γ, PPAR-γ)介导型、组成型雄甾烷受体介导型和孕烷 X 受体(pregnaneX receptor, PXR)[25,26]。

CYP450 有 50 多个亚型,是人体内主要的药物代谢酶,在中国人群中发现 CYP3A4 有 3 个点突变 CYP3A4-4, CYP3A4-5 和 CYP3A4-6,这些点突变可能影响到 CYP3A4 的活性。P450 系统主要有 CYP1A2、2A6、2B6、2C、2D6、2E1 和 3A 等,其中 CYP1A2 是 P450 酶系重要的亚族属于 CYP1 家族中的 CYP1A 亚族, CYP1A2 基因编码,主要在肝脏中特异性表达,约占肝脏 CYP 酶总量的 15%,居肝脏各 CYP 酶含量的第三位, CYPIA2 活性存在很大的

个体间差异,其遗传多态性有可能会影响个体的易感性,且在发挥代谢功能的同时容易受到外界物质的诱导或抑制从而使酶的活性受到影响,不同个体间其含量与活性差异可高达60倍以上,现已发现CYP1A2参与许多类固醇激素的代谢与活化过程,有明显的种族差异和个体差异[27]。而且,Kaneshiro等[28]最近的研究也发现P450 3A的低活性是股骨头坏死的一个致病因素,并报道药物代谢酶CYP450的其他亚型如CYP2D6和CYP2C19也与酒精性股骨头坏死有关;中国人群中CYP450的基因多态性与酒精性股骨头坏死的相关性有待进一步研究。

4 酒精性股骨头坏死与CYP450 PPAR-γ的关系

酒精导致股骨头坏死已被临床医生所重视,Jones[29]认为成人每周饮酒不少于400 ml累计饮用150 L即可发病,在股骨头坏死的病例中31.8%患者有长期酗酒史;在酒精性股骨头坏死的股骨近端处取得的骨髓间充质干细胞,其增殖分化能力下降,说明酒精在骨坏死的发病中可能起到一定作用,然而并不清楚酒精对骨髓间充质干细胞影响的明确机制[30,31]。

骨髓基质系统是由骨髓基质细胞(marrow stromal cells,MSCs)及胞外基质组成的一个网格组织。MSCs中含有高度增殖及多向分化能力的多能基质干细胞。干细胞可以再分化为成纤维细胞、网状细胞、脂肪细胞、成骨细胞、成软骨细胞以及成肌细胞等对造血微环境所必需的多种基质细胞[32]。而且研究发现,过氧化物酶体增殖子活化受体-γ(Peroxisome Proliferator-activated receptor-γ, PPAR-γ)是一种成脂转录因子,如果它表达就可以分化为脂肪细胞,否则可抑制MSCs的成脂分化,促使MSCs向新的骨细胞转化,保持MSCs正常的成骨分化功能,因此PPAR-γ在诱导MSCs成脂成骨分化过程中具有关键性调节作用[33,34]。在酒精的刺激下PPAR-γ变为活化基因,可促使脂肪前体细胞成熟并转化为脂肪细胞。李月白[35]等观察到酒精组脂肪细胞数量和成脂转录因子PPAR-γmRNA表达均明显增高,出现大量脂肪细胞,骨髓基质干细胞PPAR-γ在酒精的刺激下被活化后,成骨细胞数量减少,骨细胞内脂质沉积,供血障碍,发生脂肪变性坏死[36,37]。当骨髓基质干细胞分化为脂肪细胞的时候,干细胞池则不能提供足够的成骨细胞修复骨坏死;而股骨头是个半密闭腔隙,当酒精诱导MSCs分化为脂肪细胞时,造成髓内脂肪堆积引起骨内高压,静脉回流障碍,动脉灌注量减少,血流淤滞,导致股骨头坏死[38]。

5 展望

目前,酒精性股骨头坏死的病机尚不完全清楚,其中细胞色素P450基因多态性是酒精性股骨头坏死易感的一个重要方面,很多外源性化合物进入体后,都经过肝脏代谢,而肝药酶P450是肝代谢药物的主要酶系,其同工酶能代谢化合物使其失活,也能使某些无活性的物质转化成活性物质而产生药理作用或毒性。其中CYP2D6与CYP1A1是细胞色素P450酶系,同属于第一相反应[39],人类CYP1A1基因定位于染色体15q22-24,编码芳香烃羟化酶(AHH),在多环芳香烃(PAH)和芳香胺的代谢中发挥重要的作用,研究发现CYP1A1的T6235C位点突变可以增加酶的活性,提高酶的诱导性[40];过氧化物酶体增殖子活化受体-ϒ(PPAR-ϒ)是CYP450诱导方式的其中之一,现在对其引起酒精性股骨头坏死的研究也最多,CYP450的其他诱导方式研究还较少,能够深入研究CYP450的诱导方式及其他亚型及其基因多态性与酒精性股骨头坏死的相关性,有利于揭示酒精性股骨头坏死的发病机制。

许多临床及科研工作者发现酒精与股骨头缺血性坏死有着密切关系。因此,就酒精性股骨头坏死而言,其流行病学调查显示遗传、环境等因素与发病有着密切的联系,从CYP450酶系研究酒精性股骨头坏死的发生和变化规律与人体基因多态性的相关性,有利于揭示酒精性股骨头坏死的发病原因,深刻认识酒精性股骨头坏死的本质,为酒精性股骨头坏死的预防和治疗提供科学和理论依据。

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(收稿日期: 2011-11-18)

酒精性股骨头缺血性坏死与CYP450关系研究进展

作者： 李盛华， 孙凤歧， 周明旺， 郭铁峰， 穆欢喜， LI Shenghua， SUN Fengqi， ZHOU Mingwang， GUO Tiefeng， MU Huanxi

作者单位： 李盛华,周明旺,LI Shenghua,ZHOU Mingwang(甘肃省中医院,兰州,730050)， 孙凤歧,郭铁峰,穆欢喜,SUN Fengqi,GUO Tiefeng,MU Huanxi(甘肃中医学院,兰州,730000)

刊名： 中国骨质疏松杂志 ISTIC

英文刊名： Chinese Journal of Osteoporosis

年，卷(期)： 2013,19(7)

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