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·综述·

TAA可能诱发骨与关节病变

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摘要：我国是世界上老年人口最多的国家，其数量占到了世界老年人口总量的五分之一。随着老年人口数量的持续增加，特别是肥胖老年人口的增多，骨与关节退行性疾病人群剧增。骨与关节退行性病变成为医学界关注的焦点之一，然而其临床治疗仍是难题，这个问题在进入老龄化的中国显得尤为重要。目前，很多研究退行性病的实验没有合适的动物模型，治疗骨与关节退行性变困难的原因之一是没有合适的动物模型进行药物的筛选。硫代乙酰胺(TAA)诱导的肝纤维化动物模型稳定且重复性较好，因此该药是制备肝纤维化动物模型的常用化学药剂，而本实验室在动物实验中发现TAA可以导致试验动物骨及关节的病变，也有不少文献报道TAA在诱发肝纤维化的同时可导致骨质的破坏，因此，我们推测可以通过TAA建立一种骨与关节退行性病变的动物模型。建立TAA诱发骨与关节退行性变动物模型不仅可以证实TAA导致骨与关节病变的因果关系，并能为研究骨与关节退行性病变的发病机制、临床治疗等提供研究平台；更能引发自然界中TAA的存在、转化形式、进入人体的途径、在人体特异蓄积部位以及对人体各器官的危害等重大社会环境问题的探讨。

关键词：骨与关节退行性变；硫代乙酰胺；动物模型

TAA may induce bone and joint diseases

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Abstract: China is country that has the most elderly population in the world, accounting for one-fifth of the total elderly population of the world. As the elderly population, especially the elderly obesity population, continuously increases, the number of people with bone and joint degenerative diseases increases greatly. Bone and joint degenerative disease is one of the focuses in the medical field, but its clinical treatment is still a difficult problem. This problem is especially important in China, which the population is going into aging. At present, no appropriate animal model is suitable for the study of degenerative diseases, which is one of the causes for the difficulty of drug screening in the treatment of bone and joint degenerative diseases. Thioacetamide (TAA) induces liver fibrosis with stable and reproducible characteristics, so the drug is used in the preparation of liver fibrosis animal model commonly. Our laboratory found in animal experiments TAA leads to bone and joint disease in experimental animals. Many reports in the literatures show that TAA leads to bone destruction while it induces liver fibrosis. Therefore, we speculate that a bone and joint degeneration animal model can be established by using TAA. The establishment of TAA-induced bone and joint degeneration animal model can not only confirm the relationship between TAA and bone and joint diseases, but also provide a research platform for the study of pathogenesis and clinical treatment of bone and joint degenerative disease. The existence of TAA in nature, its transformation form, pathways into the body, accumulation parts in the body, the damage to the human organs, and social environmental issues can also been investigated.

Key words: Bone and joint degenerative diseases; Thioacetamide(TAA); Animal model

我国是世界上老年人口最多的国家，其数量占到了世界老年人口总量的五分之一。按照国际标准，我国早已于1999年进入老龄化社会。据统计，我国65岁以上老年人骨关节疾病患病率高达80%~90%[1]。随着老年人口数量的持续增加，特别是肥胖老年人口的增多，骨与关节退行性疾病人群剧

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增。骨与关节退行性病变得到了我国乃至全球医学界的广泛关注,然而,其临床治疗始终是个难题。目前,骨与关节退行性疾病已经成为老年人的常见病和多发病之一,成为继心脑血管疾病、糖尿病、恶性肿瘤三大慢性病之后对人类威胁最广泛的疾病,严重危害到了老年人的健康和生活质量。2013年4月,空军总医院骨科主任伍骥教授在"骨与关节退变防控论坛"中指出,骨与关节疾病的门诊量仅次于感冒,其死亡率仅次于恶性肿瘤,该病引起的疼痛和致残对老年人生活状态的影响是持久性的,将对我国的社会与经济发展产生长远的影响。治疗骨与关节退行性变困难的原因之一是没有合适的动物模型进行药物的筛选。

1 骨与关节退行性病变的表现

骨与关节退行性病是以反复发作的关节疼痛和关节活动障碍为主的慢性退行性病变,其病理变化主要发生在活动关节,特别是负重关节的退行性疾患表现突出[2,3]。骨与关节退行变的病理特点为关节软骨变性、软化、弹性丧失、裂碎和脱落。软骨内骨化形成关节边缘的骨赘,关节中央软骨因磨损甚至消失,关节外围软骨可出现肥厚和增生,使关节腔变狭和不平、骨端变形。关节疼痛是该类病的主要症状,气候变化时疼痛加重,活动时关节可发出粗糙的磨擦声[4-6]。这些症状可随着病理变化的加剧而加重。除疼痛外,局部关节出现肿胀、渗液并伴有肌肉萎缩,甚至出现关节畸形,严重的可以导致骨折[7,8]。在人体关节中,膝、髋关节除了支撑全身重量外,还要作多种活动,所以膝、髋关节退行性骨关节病最为常见[9]。西医认为,骨与关节退行性变是多因性的疾病,与衰老、遗传、内分泌、肥胖、免疫和机械损伤等有关[10]。然而,除了衰老和机械损伤是公认的危险因素外,其他致病因素尚无充分的实验依据。中医却对骨与关节退行性疾病有不同的理解,认为肾主骨、肝主筋,肝肾亏损则不能养骨荣筋。所以,中医认为骨与关节退行性疾病是因为肝肾虚亏、筋骨失养、长期劳损、气滞血瘀、风寒湿邪痹阻经脉所致[11]。尽管如此,中、西医目前尚无法确切阐明骨与关节退行性疾病的直接原因。

2 TAA与骨与关节退行性病变关系

TAA是急、慢性肝损伤、肝纤维化常用的致毒剂[12],被认为是研究肝纤维化的主要诱导剂,但是有文献报道在应用TAA制备肝硬化动物模型时发现动物出现不同程度的骨质损害,生活中也有似与TAA有关的骨质变化的案例。日常生活中人们可以通过接触电镀添加剂、照相药品、农药以及染色助剂等接触到TAA,因此TAA在生活中的存在形式可能是多样的,进入人体的方式也无法明确。

早在1984年,日本学者Lassila等[13,14]就发现了TAA诱发的肝损伤伴有血清蛋白和牙槽骨的变化。1996年,Nakano等[15]用四氯化碳(CCl_4)和TAA制备肝硬化模型时也提出,TAA会造成肝性骨营养不良。2013年,Kadir[16]还发现,TAA可以引起肾脏的损害。这似乎印证了中医关于肝肾亏虚导致筋骨失养的理论。无独有偶,2004年金陵晚报[17]报道了南京市代谢性骨病防治研究中心林华主任接诊7例强烈怀疑因染发引起的骨质疏松病例,最严重的2例甚至出现了股骨头坏死 体检显示,7位患者中没有雌激素水平下降、糖尿病、内分泌等疾病,可是这些患者都有一个共同点,就是在出现骨质疏松的半年内曾经染发。而且,对患者采取了剃光所染头发的紧急处理措施后,这些患者的病情不再继续发展。更有甚者,有报道称美发师夫妇生下了畸形海豹儿,巧合的是,齐玉娟等[18]也发现,TAA不但损伤斑马鱼的肝脏,还会引起幼鱼体型畸变。综合上述案例,我们有理由猜想:TAA除了引起肝、肾损害外,还具有破坏骨质的作用[19];染发可能是导致骨质疏松、引起骨与关节损害的一个诱因,染发助剂中的硫代乙酰胺可能是其中一个因素。TAA导致的肝肾损害、脂肪代谢障碍[20]甚至对脑部的影响[21]让人怀疑,TAA诱发的肝硬化是否直接导致动物的衰老,骨质损害是其表象之一?TAA与骨质损害、肝脏损害和衰老之间存在直接还是间接的关系?

3 骨与关节退行性变的动物模型

目前,很多研究退行性病的实验没有合适的动物模型,某些退行性病只得借用现有的动物模型,如研究神经退行性病变使用的是老年性痴呆的动物模型[22]。用于研究骨关节病变的动物模型除了机械制动方式外,还有手术制备的方式[19]、关节内注射[23]、自发动物模型[24]和转基因动物模型[25]等。上述动物模型的诱发机制各不相同,帮助研究者了解骨与关节退行性病除了和年龄、负重因素有关外,还和激素水平、关节生物力学紊乱、骨密度等多种因素密切相关[26,27],但与骨与关节自然发生的退行性病变存在差异,骨与关节退行性病变的相关基因仍不明确,基因转入、表达的有效性及其调控机制仍不

完善。目前,针对原因复杂的骨与关节退行性病变的动物模型,还没有在各个方面完全与人类骨与关节退行性变临床表现一致的,显然,单纯的关节注射也不能解决全身关节病变的问题[28]。

四氯化碳(CCl_4)诱导肝纤维化模型的方法被研究者视为经典方法,其与TAA引发肝纤维化的作用机制不同,因TAA诱导的肝纤维化动物模型与人类肝纤维化相似,所以适用于临床基础研究[29],而用TAA造模导致的骨损伤易被忽视。根据TAA导致骨与关节病变的种种案例,我们假设TAA导致骨与关节退行性变可以通过建立动物模型来证实。利用对骨与关节退行性疾病直接病因的认知,使用化合物诱导动物身上产生与人退行性疾病一样的病理现象,有可能在此基础上开发出更有效的预防药物乃至治疗性药物,也可以避开体外筛选的缺陷,该模型将不仅仅是根据骨质的变化建立的一种新型诱发骨与关节退行性病动物模型,还将是对中医学肝肾虚亏、筋骨失养理论的验证。

4 展望

骨与关节退行性疾病在老年人群多发,TAA可能通过哪些途径进入老年人体内目前还不是十分清楚。西医以为骨与关节疾病发病率与衰老、内分泌、体重和机械损伤相关,而中医认为骨与关节疾病是因为肝肾虚亏、筋骨失养所致,TAA在诱导肝纤维化时导致的骨质变化是否可以理解肝脏和骨损伤之间有什么必然的联系?TAA导致的骨与关节损伤动物模型的建立可能可以为我们解答这些问题。用TAA诱发的模型也许能为骨与关节退行性病研究提供仿生的研究模型,为开发和研究预防和/或治疗性药物提供体内、外研究平台;更能引发自然界中TAA的存在、转化形式、进入人体的途径、在人体特异蓄积部位以及对人体各器官的危害等重大社会环境问题的探讨。本实验室正在对应用TAA制备骨与关节退行性变的动物模型做全面且深入的研究,有望得出更多有价值的实验数据。

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