·抗代谢性疾病药物研究专栏·

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不同方法建立长期慢性高尿酸血症模型及对相关并发症影响的研究进展

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摘 要: 高尿酸血症(hyperuricemia, HUA)在人类中具有较高的发病率, 且其与痛风性关节炎、Ⅱ型糖尿病、心血管疾病以及肝肾功能损伤等多种疾病的进程密切相关。实验动物研究显示, HUA 相关并发症需要长期稳定的诱导过程。与人类不同的是, 常用模式动物具有较高的尿酸酶表达, 可迅速将尿酸分解成可溶性尿囊素排泄出体外, 该特点易造成造模期间高尿酸日均暴露时间不足。因此, HUA 相关并发症的观察对实验模型在模式动物、诱导方式、高尿酸暴露时间等方面均有较高的要求。本文对 HUA 动物模型造模方法以及不同造模方法对慢性并发症的影响进行综述, 重点从主流药物造模方法的优劣分析、模式动物的选择、基因干预造模 3 个方面展开, 为 HUA 长期并发症研究的造模方法选择提供参考依据。

关键词: 高尿酸血症(HUA); 造模; 并发症

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Research Progress in Long-term Chronic Hyperuricemia Modeling Methods and Their Impacts on Associated Complications

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Abstract: Hyperuricemia (HUA) is a common disease associated with the incidence and development of multiple complications such as gouty arthritis, type 2 diabetes, cardiovascular disease, functional liver and kidney injuries. Long-term and stable induction is essential for HUA-associated complications in modeling animals. Unlike in human, common model animals express high levels of uricase that decompose uric acid to soluble allantoin for renal excretion. This profile leads to insufficient daily exposure to high uric acid levels during modeling period. Therefore, the model animal selection, induction method and high uric acid duration are all causes that influence the observation of hyperuricemia-associated complications. Herein, the research progress in modeling of long-term chronic HUA animals and evaluation of the associated complications is reviewed. It mainly focuses on evaluation of current chemical inducers, selection of modeling animals and influence of genetic intervention, in order to provide information for modeling method selection in long-term chronic HUA research.

Key words: hyperuricemia (HUA); modeling; complication

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高尿酸血症(hyperuricemia, HUA)是机体内尿酸生成过多或/和排泄障碍造成的尿酸体内积聚的现象。2019 年中华医学会内分泌学分会发布的《中国高尿酸血症与痛风诊疗指南》指出, 非同日、

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2 次空腹血尿酸大于 420 μmol/L (成年人, 不分男性、女性)即可诊断为 HUA[1]。国内外流行病学数据显示, HUA 发病率呈逐年升高且年轻化趋势[2~3]。长期 HUA 可诱发多种并发症, 如痛风[4]、Ⅱ型糖尿病[5]、心血管疾病[6~7]、肝肾功能损伤[8~9]等。当前应用的 HUA 动物模型大多数为考察尿酸体内生成和排泄, 这仅需要动物短期维持高水平尿酸即可达到研究目的。然而, HUA 相关并发症是长期高尿酸慢性诱导作用下的结果。为更真实模拟和研究人体 HUA 并发症的病理诱导过程, 构建长期、稳定的 HUA 动物模型显得尤为重要。本综述从主流药物造模方法、模式动物选择和基因干预造模 3 个方面, 对当前 HUA 模型构建方法的长期应用进行优劣评价, 并展望新型模型和技术的未来发展方向, 为今后 HUA 长期并发症体内研究的模型选择提供参考。

1 主流药物造模方法的优劣分析

1.1 用于 HUA 造模的药物及其作用机制

当前, 大部分实验使用较多的造模方法仍是以通过药物干预为主的方式增加尿酸来源、抑制尿酸代谢及排泄, 主要造模药物包括氧嗪酸钾(potassium oxonate, PO)、次黄嘌呤(hypoxanthine, HX)、腺嘌呤(adenine, AD)、乙胺丁醇(ethambutol, EMB)、烟酸(nicotinic acid, NA)、果糖(fructose, FRU)、酵母(yeast, YE)等。文中汇总了这些造模诱导剂[10~24]的机制、给药方式, 并对成模性进行评价(表 1)。根据造模药物的作用机制, 现有的研究提示, 基于氧嗪酸钾和次黄嘌呤的模型更有利于评价尿酸的生成以及重吸收[25~27], 而基于腺嘌呤的模型更有利于评价 HUA 下的肾脏损伤及干预保护[18, 28], 基于果糖的模型更有利于评价 HUA 合并糖尿病等代谢性紊乱的机制及改善效应[29~30]。单独应用乙胺丁醇及烟酸诱导 HUA 鲜有报道, 其常与外源性尿酸前体物质联合诱导[19~20]。

1.2 联合造模在慢性 HUA 并发症中的应用

HUA 并发症的自发性诱导需要维持组织器官每日的高尿酸暴露时间以及诱导周期。由于非灵长类哺乳动物大都表达尿酸酶, 当诱导剂代谢或排泄后, 实验动物体内的尿酸水平迅速回落[31]。单一诱导剂往往难以观察到并发症现象, 在当前研究中, 人们常常需使用两种以上的联合造模剂诱导组织器官的慢性病变。联合药物诱导 HUA 并研究其并发症的模型较多, 并无均一标准, 鲜有文献系统性评价方法的适用性。我们整理了现有联合造模诱导方法[32~38]对尿酸水平以及并发症的诱导效果(表 2), 发现在联合造模模型药物选择中, 氧嗪酸钾是绝大多数实验的选择, 其联合腺嘌呤、次黄嘌呤、酵母膏在尿酸升高倍数上均有较好的表现。但是, 当前关于 HUA 并发症的研究多集中于肾脏损伤, 对其他组织器官损伤的模型探索较少。

2 模式动物选择

由于生理病理过程与人类相似且饲养方便, 大多数研究选择啮齿类动物作为 HUA 的模式动物, 包括 SD 大鼠、昆明小鼠和 C57 小鼠等。然而, 不同于人类的是, 这些动物均能合成尿酸酶, 在体内将尿酸代谢为可排泄的尿囊素[31]。这一特征正是当前药物诱导剂造模难以保证组织器官长期持续性高浓度尿酸暴露的原因, 这亦使得相关并发症难以被观察到。

表 1 HUA 造模常用药物及成模性评价

Table 1 Commonly used chemical inducers for HUA and the modeling ability

Inducer	Mechanism	Route	Model evaluation	Reference
PO	Uricase inhibitor that prevent UA converting to allantoin	ig	Unstable	[10]
		ip	Stable, short duration	[11~12]
HX	Biosynthetic precursor of UA	ig	Stable, short duration, limited UA increasing	[13]
		ip	Stable, short duration, limited UA increasing	[13~14]
AD	Convert to 2,8-dihydroxyadenine, which disrupt renal function	ig	Stable, kidney toxicity	[15~17]
EMB	Competition of excretion to reduce UA excretion	ig	Stable, compatible use with AD	[18~19]
NA	Competition of excretion to reduce UA excretion	ig	Stable, compatible use with HX	[20~21]
FRU	Promote ATP depletion and enhance purine metabolism	Drinking/feeding	Limited UA increasing	[22]
YE	Increase XOD activity to promote UA synthesis	ig/feeding	Compatible use with other inducers	[12, 23~24]

注: UA, 尿酸; ATP, 三磷酸腺苷; XOD, 黄嘌呤氧化酶; ig, 灌胃; ip, 腹腔注射。

Notes: UA, uric acid; ATP, adenosine triphosphate; XOD, xanthine oxidase; ig, intragastric administration; ip, intraperitoneal injection.

表 2　联合造模对 HUA 并发症的诱导效果

Table 2　Induction effects of combined chemical inducers on HUA-associated complications

Complication	Species	Modeling method	Duration	Fold change	Reference
Liver, kidney injury with gouty arthritis	SD rats	2% PO + 12% YE feeding	5 weeks	1.61	[32]
Kidney injury	KM mice	PO 200 mg/kg (ig) + AD 50 mg/kg (ig)	21 days	2.80	[33]
Kidney injury	KM mice	PO 300 mg/kg (ip) + HX 300 mg/kg (ig)	7 days	1.89	[34]
Kidney injury	KM mice	AD 100 mg/kg (ig) + EMB 250 mg/kg (ig)	6 weeks	2.45	[35]
Kidney injury	KK-Ay mice	PO 250 mg/kg (ip) + HX 300 mg/kg (ig)	8 weeks	≈4.00	[36]
Myocardial injury	KM mice	AD 100 mg/kg (ig) + EMB 250 mg/kg (ig)	33 days	≈3.50	[37]
Blood vessel injury	SD rats	PO 10 mg/kg (ip) + 10% YE feeding	36 days	≈2.10	[38]

相比而言, 禽类的嘌呤代谢途径与人类更为相似, 其仅需在基础饲料中添加次黄嘌呤、酵母等尿酸前体物质或腺嘌呤影响尿酸排泄即可诱导稳定的 HUA 模型。当前, 常用的以禽类为主的 HUA 模型主要选择鸡或鹌鹑作为模式动物。在雄性迪法克鹌鹑饲料中添加 15 g/kg 的酵母粉, 饲喂 140 天后血清尿酸水平显著性升高, 在第 60 天时研究人员可检测到血清甘油三酯水平的显著性上升, 第 90 天时血清葡萄糖水平呈现显著性上升。同时, 该模型中血清黄嘌呤氧化酶以及胰岛素水平均显著性升高, 这是机体氧化应激以及胰岛素耐受的表现, 也是多器官损伤的病理基础。然而, 在该研究总计 140 天的实验周期中, 肝肾功能的显著性变化并未被观察到[39]。该模型的规律与人类饮食结构规律改变类似, 可用于模拟自然慢性损伤, 但其存在实验周期过长的缺点。近年来有研究表明, 在高脂高嘌呤饮食的基础上皮下注射氧嗪酸钾 200 mg/kg 可进一步提升鹌鹑血清尿酸水平约 1.5 倍, 且在 14 周后可观察到主动脉壁的脂质沉积、斑块形成, 以及肾小球的脂质沉积和肾小管的空泡变性[40]。这说明通过进一步提高尿酸水平可加速 HUA 并发症进程。然而, 当前大多数实验室缺乏进行禽类饲养的条件, 在模型推广上或许有一定难度。

近年来, 基于斑马鱼的疾病模型受到广泛关注, 斑马鱼与人类基因高度同源, 生物结构与生理功能和人类亦高度相似, 且其有易于繁殖、实验周期短、实验药量小、给药方式简单的优点。当前, 基于斑马鱼的 HUA 模型尚处于摸索的起步阶段。研究显示, 使用 200 μmol/L 氧嗪酸钾联合 10 μmol/L 黄嘌呤可提升斑马鱼体内尿酸水平约 2 倍, 该方法可作为急性 HUA 模型[41], 该模型可应用于化合物的降尿酸效果的快速评估[42]。然而, 作为新兴模式动物, 当前斑马鱼的 HUA 造模方法缺乏长期慢性状态下的有效性评估。

灵长类动物的尿酸合成代谢途径与人类最为相似, 但由于其饲养难度大以及实验成本高昂, 鲜少用于 HUA 相关研究。近期研究显示, 给予雄性恒河猴 200 mg/kg 肌苷腹腔注射 1 h 后, 血清尿酸浓度提高约 4 倍; 然而, 4 h 后血清尿酸即回落至基线[43]。该方法并不适用于长期慢性 HUA 及相关并发症影响的评估。

3　基因干预造模

3.1　当前针对 HUA 的基因干预靶点

尿酸在动物体内可在尿酸酶作用下降解为可溶性尿囊素排出体外, 或通过肾脏和肠道排泄。因此, 当前基因干预靶点主要分布于编码尿酸酶的 *UOX* (*urate oxidase*)、负责肾脏重吸收的 *URAT*1 (*urate transporter* 1)和 *GLUT*9 (*glucose transporter* 9), 以及负责肠道排泄的 *ABCG*2 (*ATP-binding cassette transporter*, *subfamily G*, *member* 2)[44]。近年, 基于全基因组关联的研究显示, GLUT12 (glucose transporter 12)是一种生理性尿酸盐转运蛋白, 其功能障碍会导致血尿酸浓度的升高, 提示其或许可以作为新的干预靶点[45]。此外, 在肠道排泄中, *PDZK*1 (*PDZ domain-containing* 1)和 *ABCG*2 的表达高度相关, 敲除 *PDZK*1 可间接性导致 *ABCG*2 的表达同步下调, 进而减少尿酸肠道排泄[46]。

3.2　基因干预对尿酸水平的影响

如表 3 所示, 当前研究中针对 HUA 的基因干预造模所选用的小鼠以 C57BL 系列为主, 不同基因的敲除对于模型动物的获得数以及尿酸水平的提高具有较大差异[45, 47~54]。*UOX* 敲除可以使得血尿酸水平大幅升高, 然而其死亡率也较高, 因此其操作性并不强。*URAT*1 的敲除并不能使得尿酸水平显著性升高, 因此不适用于建立 HUA 模型。*GLUT*9 的敲除, 在系统性敲除和特定组织器官敲除中具有不同的效果, 系统性敲除 *GLUT*9 具有胚胎致死性, 而肝特异性敲除则没有, 且可大

表 3 基因干预对血尿酸水平的影响

Table 3 Effect of genetic intervention on blood uric acid level

Gene	Species	Fold change	Survival status	Reference
UOX	C57BL/6J	12.22	65% died within 4 weeks	[47]
UOX	C57BL/6J	3.35 (male); 2.84 (female)	About 40% die within 5 weeks; 40% live up to 63 weeks	[48]
UOX	C57BL/6J	3.40	–	[49]
*URAT*1	129Sv	1.04	–	[50]
*GLUT*9	C57BL/6J, C57BL6/N	≈2.00	10% probability via hybridization, serious intra-fetal death	[51]
Liver *GLUT*9	C57BL/6J, C57BL6/N	≈5.00	25% probability via hybridization	[51]
Intestine *GLUT*9	C57BL/6J	≈1.30	–	[52]
*GLUT*9	C57BL6/N	No differences	–	[53]
*ABCG*2	FVB	≈1.40	–	[54]
*GLUT*12	C57BL/6J	≈1.30	–	[45]

幅升高血尿酸浓度。

3.3 基因干预诱发的急慢性并发症

早在 1994 年就有研究者利用胚胎干细胞同源重组的方法构建 *UOX* 基因敲除小鼠, 在 5 周龄 *UOX* 敲除小鼠的肾脏中可见大量尿酸结晶以及肾小管急性萎缩, 这也是诱发小鼠大量死亡的原因[47]。近年, 有研究者通过 TALEN 技术进行杂合子敲除, 然后将敲除后的小鼠交配获得 *UOX* 纯合小鼠, 这种方法提升了小鼠存活率, 这些小鼠均表现出显著的肾功能障碍, 其中雄性小鼠伴有显著性的胰腺损伤以及胰岛素分泌受损, 而雌性小鼠伴有高血压以及脂代谢障碍[48]。在 *UOX* 敲除的雄性小鼠中, 辅以链脲霉素饲养可加速胰岛 β 细胞损伤及诱导糖尿病[49]。

在杂交获得的系统性 *GLUT*9 基因敲除小鼠中, 研究者观察到肾脏梗阻性结石、肾小管间质炎症和皮质的进行性炎症纤维化, 以及轻度肾功能不全[51]。与此不同的是, 在肝脏特异性敲除 *GLUT*9 后, 虽然尿酸水平出现大幅升高, 但并无显著性的肾脏以及心血管损伤[51, 55]; 在肠上皮细胞特异性敲除 *GLUT*9 后, 机体出现脂代谢紊乱、血压升高以及心脏重构的现象[52]。另有研究显示, 条件性诱导肾 *GLUT*9 敲除 1 周后, 收缩压和舒张压双重下降, 同时心率升高[53]。

4 展望

随着发病率的逐年升高, HUA 长期慢性所伴随的并发症问题亦浮出水面。当前, 大多数动物模型仅用于短期降尿酸筛选, 关于其长期并发症甚少。虽然药物联合模型在长期慢性 HUA 中具有良好的表现, 但器官损伤也多集中于肾脏, 对其他如心血管系统、代谢系统并发症鲜有提及。建立合适的长期药物造模方法并系统性评估其对多种慢性并发症的影响, 对今后 HUA 相关研究的发展具有良好助力。

当前, 大多数实验室主要选择小鼠或大鼠进行 HUA 模型构建, 而啮齿类动物由于表达尿酸酶并不是最佳的 HUA 模式动物, 因此, 今后研究人员可进一步推动其他模式动物如禽类在 HUA 相关领域的应用。由于饲养便捷且廉价, 斑马鱼被广泛用于药物筛选实验, 但其在 HUA 上的方法建立尚不成熟, 在未来条件优化后或许会有良好的表现。

通过基因干预诱导 HUA 模型是今后重要的发展方向。在当前研究中, *UOX* 敲除可引起尿酸水平的显著性升高, 然而其死亡率高且子代获得困难。其次为 *GLUT*9, 尤其是肝特异性敲除*GLUT*9 后, 实验动物在存活率以及尿酸升高倍数上均有良好表现。其实, 无论是何种敲除, 均需考虑该基因及尿酸水平对胚胎发育的影响, 在未来条件性诱导敲除或许是解决胚胎致畸致死或成年前死亡率过高的发展方向。

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