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GnRH 类似物对子宫肌瘤大鼠模型血液黏度、子宫系数和炎性细胞浸润的影响 *

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摘要 目的：探讨促性腺激素释放激素（Gonadotropin releasing hormone，GnRH）类似物对子宫肌瘤大鼠模型血液黏度、子宫系数和炎性细胞浸润的影响。**方法：**子宫肌瘤大鼠模型（n=36）随机平分为三组 - 模型组、米非司酮组与 GnRH 类似物组，分别给予腹腔注射 0.15 ml 的生理盐水、2 mg/kg 米非司酮与 2 mg/kg GnRH 类似物，每周 1 次，持续 8 周。**结果：**米非司酮组与 GnRH 类似物组治疗第 4 周与第 8 周的全血比黏度、卵泡刺激素（FSH）、黄体生成素（LH）值都低于模型组（*P*<0.05），GnRH 类似物组低于米非司酮组（*P*<0.05）。米非司酮组与 GnRH 类似物组治疗第 8 周的子宫系数、子宫白介素（IL）-10 与肿瘤坏死因子（TNF）-α 表达水平都低于模型组（*P*<0.05），GnRH 类似物组低于米非司酮组（*P*<0.05）。米非司酮组与 GnRH 类似物组治疗第 8 周的子宫内膜厚度、腺间质面积比、腺体面积与腺腔面积都高于模型组（*P*<0.05），GnRH 类似物组高于米非司酮组（*P*<0.05）。米非司酮组与 GnRH 类似物组治疗第 8 周的子宫组织 Wnt5b 与 β-catenin 蛋白相对表达水平低于模型组（*P*<0.05），GnRH 类似物组低于米非司酮组（*P*<0.05）。**结论：**GnRH 类似物在子宫肌瘤大鼠模型的应用能降低子血液黏度，还可抑制血清性激素的分泌，增加子宫系数，抑制 Wnt5b 与 β-catenin 蛋白的表达，从而可改善子宫肌瘤大鼠的炎性细胞浸润状态与子宫内膜形态。

关键词：促性腺激素释放激素；子宫肌瘤；大鼠；血液黏度；子宫系数；炎性细胞浸润

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Effects of GnRH Analogues on Blood Viscosity, Uterine Coefficient and Inflammatory Cell Infiltration in Rat Models of Uterine Fibroids*

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ABSTRACT Objective: To investigate the effects of Gonadotropin releasing hormone (GnRH) analogues on blood viscosity, uterine coefficient and inflammatory cell infiltration in rat models of uterine fibroids. **Methods:** Rat models of uterine fibroids (n=36) were equally randomly divided into three groups-model group, mifepristone group and GnRH analogue group. The three groups were given intraperitoneal injection of 0.15 mL of normal saline, 2 mg/kg of mifepristone, 2 mg/kg GnRH analogue, once a week for 8 weeks. **Results:** The values of whole blood specific viscosity, follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the 4th and 8th weeks of treatment in the mifepristone group and GnRH analog group were lower than those of the model group (*P*<0.05), the GnRH analog group were lower than mifepristone group (*P*<0.05). Uterine coefficient, uterine interleukin (IL)-10 and tumor necrosis factor (TNF)-α expression levels in the mifepristone group and GnRH analog group at the 8th week of treatment were lower than those in the model group (*P*<0.05), GnRH analog The group were lower than the mifepristone group (*P*<0.05). The endometrial thickness, gland-to-interstitial area ratio, gland area and gland cavity area of the mifepristone group and the GnRH analog group were higher than the model group at the 8th week of treatment (*P*<0.05), and the GnRH analog group were higher than that in the GnRH analog group Mifepristone group (*P*<0.05). The relative expression levels of Wnt5b and β-catenin protein in the uterine tissue of the mifepristone group and the GnRH analog group were lower than the model group at the 8th week of treatment (*P*<0.05), and the GnRH analog group were lower than the mifepristone group (*P*< 0.05). **Conclusion:** The application of GnRH analogues in rat models of uterine fibroids can reduce blood viscosity, inhibit the secretion of serum sex hormones, increase uterine coefficient, and inhibit the expression of Wnt5b and β-catenin proteins, thereby improving morphology of the endometrium uterine fibroids and the infiltration state of inflammatory cells in rats .

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前言

子宫肌瘤(uterine fibroids)为一种妇科生殖系统良性肿瘤，多发生于育龄妇女，特别是 30-40 岁妇女中其患病率占妇女良性肿瘤的 60.0 %左右[1]。子宫肌瘤患者在临床上多表现为白带异常、流产、盆腔包块、出血、疼痛等症状，也是导致很多女性不孕的主要原因，严重影响女性的身心健康[2,3]。目前，子宫肌瘤的具体发病机制还不明确，不过其增长速度受雌激素和黄体酮的影响[4]。子宫肌瘤切除术是治疗子宫肌瘤的标准治疗手段，但是任何手术都具有创伤性，从而对患者的身心可造成一定伤害[5]。现代研究表明，子宫能产生多种生物活性物质，可参与机体内生殖、内分泌、生理及病理过程，切除子宫可能诱发多种并发症的发生，为此当前在临床上多采用药物治疗 [6,7]。米非司酮(mifepristone) 是一种合成的选择性孕激素受体(Progesterone receptor，PR)调节剂，可用于治疗子宫肌瘤[8,9]。促性腺激素释放激素(Gonadotropin releasing hormone，GnRH)类似物可有效缩小子宫肌瘤的体积，也可有效抑制子宫肌瘤中所含的孕激素受体，从而减轻临床症状[10,11]。本文具体探讨了 GnRH 类似物对子宫肌瘤大鼠模型血液黏度、子宫系数和炎性细胞浸润的影响，以明确 GnRH 类似物的应用机制与价值。

1 资料与方法

1.1 动物与试剂

清洁级 SD 大鼠购自北京维通利华实验动物有限公司(批号 88234321)，体重 250-300 g，饲养于由本院实验动物中心。整个实验过程都在清洁级实验室内进行每笼 3-5 只，实验期间自由饮用灭菌蒸馏水，温度 24.0~26.0 ℃，湿度 65.0 %左右，12 h:12 h 明暗交替。清洁级饲料购自科澳协力饲料有限公司，在饲养过程中随时补充补足饲料。

GnRH 类似物购自上海丽珠制药有限公司（国药准字 H20093852），米非司酮购自湖北葛店人福药业有限责任公司（国药准字 H20033551），性激素放射免疫试剂盒购自大量 TAKARA 公司，炎症因子酶联免疫检测试剂盒购自上海茂元科技有限公司，病理染色与检测试剂盒购自美国 Neomarker 公司，抗 Wnt5b 抗体、抗 β-catenin 抗体都购自美国 sigma 公司。

1.2 子宫肌瘤大鼠模型的建立

所有大鼠都给予雌激素、孕激素负荷法建立子宫肌瘤模型：给予大鼠腹腔注射苯甲酸雌二醇[0.5 mg(kg·d)$^{-1}$]，1 次 /d；腹腔注射孕酮[4 mg(kg·d)$^{-1}$]，1 次 / 周，连续 25 d；然后给予孕酮、苯甲酸雌二醇、同时腹腔注射，1 次 /d，连续 5 d。

1.3 大鼠治疗方法

将造模成功的 SD 大鼠(n=36)随机平分为三组 - 模型组、米非司酮组与 GnRH 类似物组，分别给予腹腔注射 0.15 mL 的生理盐水、2 mg/kg 米非司酮与 2 mg/kg GnRH 类似物，每周 1 次，持续 8 周。在造模与治疗期间积极给予大鼠保温，可于大腿外侧肌肉注射青霉素抗感染。

1.4 观察指标

（1）所有大鼠在治疗第 4 周与第 8 周进行尾静脉取血 0.3 mL 左右，采用全自动血液流变快测仪测定全血比黏度。分离血清后，采用放免法检测血清卵泡刺激素(FSH)、黄体生成素(LH)含量。(2)在治疗第 8 周处死所有大鼠，剪取子宫称重，计算子宫系数，子宫系数 = 子宫质量 / 体质量，单位为 mg/g。(3)取子宫组织，研磨成匀浆，2000 rpm 离心 10 min，取上清，采用酶联免疫法检测 IL-10 与 TNF-α 水平。同时观察子宫内膜形态，包括子宫内膜厚度、腺间质面积比、腺体面积与腺腔面积等。(4)在研磨后的子宫组织加入蛋白裂解液提取总蛋白，定量总蛋白浓度后，进行 SDS- 聚丙烯酰胺凝胶将分离的蛋白转膜后采用 8.0 %的脱脂牛奶室温下孵育 2 h，分别加入抗 Wnt5b 抗体、抗 β-catenin 抗体 4 ℃孵育过夜(稀释比 1:1000)，洗涤 3 次后加入二抗，室温孵育 1 h，洗涤 3 次后进行暗室曝光，以目标条带与 β-actin 条带 A 的比值作为目的蛋白的相对表达水平。

1.5 统计方法

统计软件为 SPSS22.00，计量数据用均数±标准差($\bar{x}\pm s$)表示，两组间比较采用 t 检验，三组及以上数据采用单因素方差分析，检验水准 α=0.05。

2 结果

2.1 血液黏度与性激素表达变化对比

米非司酮组与 GnRH 类似物组治疗第 4 周与第 8 周的全血比黏度、FSH、LH 值都低于模型组(P<0.05)，GnRH 类似物组低于米非司酮组(P<0.05)。见表 1。

2.2 子宫系数和炎性细胞浸润对比

米非司酮组与 GnRH 类似物组治疗第 8 周的子宫系数、子宫 IL-10 与 TNF-α 表达水平都低于模型组(P<0.05)，GnRH 类似物组低于米非司酮组(P<0.05)。见表 2。

2.3 子宫内膜形态学对比

米非司酮组与 GnRH 类似物组治疗第 8 周的子宫内膜厚度、腺间质面积比、腺体面积与腺腔面积都高于模型组(P<0.05)，GnRH 类似物组高于米非司酮组(P<0.05)。见表 3。

2.4 Wnt5b 与 β-catenin 蛋白相对表达水平对比

米非司酮组与 GnRH 类似物组治疗第 8 周的子宫组织 Wnt5b 与 β-catenin 蛋白相对表达水平低于模型组(P<0.05)，GnRH 类似物组低于米非司酮组(P<0.05)。见表 4。

3 讨论

子宫肌瘤是最常见的子宫平滑肌肿瘤，在临床上可伴随有痛经、盆腔疼痛、贫血等症状，还是导致患者女性患者不孕的重要原因。子宫肌瘤的发病机制目前尚未明确，雌激素与孕激素都是调节肌瘤生长的重要因素[12]。现代病理学研究分析显示子宫肌瘤是卵巢依赖性肿瘤，其组织雌激素受体与局部雌激素水平高于周围正常子宫肌组织，孕激素又促进和维持子宫肌瘤细

表 1 三组治疗不同时间点的血液黏度与性激素表达变化对比

Table 1 Comparison of blood viscosity and changes in sex hormone expression in the three groups at different time points of treatment

Groups	n	Whole blood viscosity(mPa/s)		FSH(IU/L)		LH(IU/L)	
		4 Weeks	8 Weeks	4 Weeks	8 Weeks	4 Weeks	8 Weeks
GnRH analogs	12	4.65±0.45*#	4.22±0.32*#	1.53±0.22*#	1.41±0.22*#	1.09±0.22*#	0.97±0.21*#
Model group	12	5.42±0.51*	5.21±0.25*	1.78±0.14*	1.65±0.32*	1.22±0.18*	1.10±0.17*
Mefisidone group	12	5.92±0.65	5.93±0.44	2.15±0.22	2.14±0.19	1.36±0.23	1.37±0.18
F		8.832	10.003	7.894	9.135	6.882	7.333
P		0.002	0.000	0.010	0.001	0.020	0.015

Note: Compared with the model group, *P<0.05; compared with the mifepristone group, #P<0.05.

表 2 三组治疗第 8 周的子宫系数和炎性细胞浸润对比

Table 2 Comparison of uterine coefficients and inflammatory cell infiltration at week 8 of the three treatment groups

Groups	n	Uterine coefficients	IL-10(μg/L)	TNF-α(μg/L)
GnRH analogs	12	3.29±0.22*#	14.98±2.88*#	19.77±2.57*#
Model group	12	4.56±0.72*	19.87±3.10*	26.73±5.19*
Mefisidone group	12	7.62±0.32	24.58±2.48	36.38±4.15
F		10.774	12.422	13.333
P		0.000	0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the mifepristone group, #P<0.05.

表 3 三组治疗第 8 周的子宫内膜形态学对比

Table 3 Endferior endometrial morphological comparison at week 8 of treatment in the three groups

Groups	n	Enseminal thickness(μm)	Admiral interstitial area ratio	Adenal Area(μm²)	Glandular cavity area(μm²)
GnRH analogs	12	67.73±3.82*#	0.48±0.02*#	565.33±64.32*#	167.7±31.82*#
Model group	12	59.52±4.28*	0.33±0.03*	471.71±57.64*	129.5±38.13*
Mefisidone group	12	37.37±3.46	0.19±0.08	379.13±61.92	91.43±18.33
F		21.492	11.742	33.292	23.721
P		0.000	0.000	0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the mifepristone group, #P<0.05.

表 4 三组治疗第 8 周的子宫组织 Wnt5b 与 β-catenin 蛋白相对表达水平对比

Table 4 Comparative expression levels of Wnt5b and β-catenin protein in the uterine tissues at week 8 of the three treatment groups

Group	n	Wnt5b	β-catenin
GnRH analogs	12	1.87±0.21*#	1.77±0.27*#
Model group	12	3.18±0.15*	2.18±0.16*
Mefisidone group	12	4.26±0.33	3.72±0.22
F		24.094	19.884
P		0.000	0.000

Note: Compared with the model group, *P<0.05; compared with the mifepristone group, #P<0.05.

胞上雌激素含量，雌激素能增加肌瘤细胞中孕激素受体含量，从而间接刺激子宫肌瘤的生长，也容易诱发子宫内膜增生的发生[13,14]。子宫肌瘤的发生与内分泌紊乱、功能低下等存在相关性，特别是血液黏度异常与炎性细胞浸润可引起子宫肌层增厚，促使肌瘤产生[15,16]。

现代研究表明 GnRH 类似物还可使子宫肌瘤与动脉内的血管血流量减少，缩小子宫肌瘤体积，从而抑制肌瘤的生长[17,18]。GnRH 类似物可抑制垂体分泌促性腺激素，抑制肌瘤组织生长，降低血清中性激素的水平和促进肌瘤细胞凋亡，可减轻子宫肌瘤导致的子宫组织病理损伤[19,20]。本研究分析了 GnRH 类似物对子宫肌瘤大鼠模型血液黏度、子宫系数和炎性细胞浸润的影响，结果显示：治疗第 4 周与第 8 周后，米非司酮组与 GnRH 类似物组的全血比黏度、FSH、LH 值都低于模型组，GnRH 类似物组低于米非司酮组（P<0.05），表明 GnRH 类似物

的应用能降低子宫肌瘤大鼠的血液黏度,还可抑制血清性激素的分泌,结合 Feng Y[21]和 Hamza MS[22]等研究分析其原因在于--GnRH 类似物可与 GnRH 竞争 GnRH 受体,其持续应用可抑制 LH 和 FSH 的合成与释放,改变受体后效应,从而可使 GnRH 受体发生降调节。

在子宫肌瘤的发生发展过程,雌激素受体与孕激素受体发挥关键作用,子宫肌瘤组织内雌激素受体与孕激素受体表达水泡高于周围正常肌组织,两者共同发挥作用促进肌瘤的生长与发展[23,24]。本研究显示子宫肌瘤大鼠均表现细胞体积增大,细胞器数目增多,细胞内出现丰富的有致密小体的肌微丝,肌细胞处于高度增生活跃状态,胶原纤维增生紊乱堆积[25]。正常情况下,IL-10 在体内浓度较低,具有促进细胞生长分化、调节免疫应答等多种生物学效应。TNF-α 为一种促炎因子,高浓度的 TNF-α 具有致热、致炎等病理作用,还使局部平滑肌组织细胞损伤及增生病变加剧,进而导致子宫肌细胞增生肥大,形成肌瘤[26,27]。本研究显示米非司酮组与 GnRH 类似物组治疗第 8 周的子宫系数、子宫 IL-10 与 TNF-α 表达水平均显著低于模型组(P<0.05),GnRH 类似物组显著低于米非司酮组(P<0.05);治疗第 8 周,米非司酮组与 GnRH 类似物组的子宫内膜厚度、腺间质面积比、腺体面积与腺腔面积均显著高于模型组(P<0.05),GnRH 类似物组显著高于米非司酮组(P<0.05),表明 GnRH 类似物的应用能抑制子宫肌瘤大鼠的炎性细胞浸润,改善子宫内膜形态,从机制上分析,米非司酮可以有效抑制子宫肌瘤中所含的孕激素受体,降低与肌瘤有关的疼痛等。同时减轻肌瘤的压力症状与 Mynbaev OA 等[28]研究结果类似。

近年来研究发现,子宫肌瘤患者中 Wnt5b 与 β-catenin 蛋白呈现高表达水平,Wnt5b 与 β-catenin 参与和调节机体的生理功能,是神经 - 内分泌 - 免疫网络中的重要递质,也可传递细胞网络间的生物信息,降低免疫细胞的分泌功能和吞噬杀伤能力[29]。当前有研究表明肌瘤组织比邻近肌层中 Wnt5b 与 β-catenin 蛋素受体 mRNA 表达水平均有增加,也使得增殖抗原 Ki-67 表达量升高[30,31]。本研究显示米非司酮组与 GnRH 类似物组治疗第 8 周的子宫组织 Wnt5b 与 β-catenin 蛋白相对表达水平低于模型组(P<0.05),GnRH 类似物组低于米非司酮组(P<0.05),表明 GnRH 类似物的应用能抑制子宫肌瘤大鼠 Wnt5b 与 β-catenin 蛋白的表达,当前有研究[32-34]表明,GnRH 类似物能改善机体内分泌环境有关,可显著降低机体内雄激素水平、血糖水平,从而达到抑瘤的目的,与本研究结论一致。本研究不足之处在于:受经费与研究时间的限制,没有纳入空白对照组,观察的时间点比较少,也没有进行剂量学分析,将在后续研究中探讨。

综上所述,GnRH 类似物在子宫肌瘤大鼠模型的应用能降低其血液黏度,还可抑制血清性激素的分泌,增加子宫系数,抑制 Wnt5b 与 β-catenin 蛋白的表达,从而可改善子宫肌瘤大鼠的炎性细胞浸润状态与子宫内膜形态。

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