

doi: 10.13241/j.cnki.pmb.2020.10.006

κ 阿片受体选择性激动剂 U50488H 对大鼠心房纤维化及 缝隙连接蛋白 43 重构的影响 *

鲍宏刚¹ 苏芳菊² 徐志勇¹ 朱立强¹ 薛 丽¹ 杨海青^{1Δ}

(1 中部战区空军医院心内科 山西 大同 037000; 2 联勤保障部队解放军 940 医院心内科 甘肃 兰州 730000)

摘要 目的:观察 κ 阿片受体选择性激动剂 U50488H 对大鼠心房纤维化及缝隙连接蛋白 43 重构的影响。方法:40 只 SPF 级雄性 wistar 大鼠(180±20 g)随机等分为 4 组:对照组、盐酸异丙肾上腺素(isoprenaline ISO)[5 mg/(kg·d)](ISO 组)、ISO[5 mg/(kg·d)]+U50488H[1.5 mg/(kg·d)]组(U50488H 组)、ISO[5 mg/(kg·d)]+Nor-BNI(κ 阿片受体阻断剂)[2 mg/(kg·d)]+U50488H[1.5 mg/(kg·d)]组(Nor-BNI 组)。每组每天 1 次给予相应试剂,7 d 后处死大鼠。H-E 染色法观察心肌纤维化情况;Masson 染色法计算胶原容积分数;免疫组化 SP 法观察 Cx43 分布,并进行半定量分析;Western blot 检测 Cx43 蛋白的表达。结果:① HE、Masson 染色结果示对照组无明显心房纤维化,ISO 组出现明显的纤维化,而 U50488H 组较 ISO 组心房纤维化程度均减弱(P 均 <0.01),其效应可被 Nor-BNI 抑制。② Cx43 含量在 ISO 组较对照组均减少(P 均 <0.01),分布无规律性,侧面分布相对增多,U50488H 组中 Cx43 含量减少程度较 ISO 组减弱($P<0.01$),且分布较规律。其效应可被 Nor-BNI 阻断。结论:κ 阿片受体选择性激动剂 U50488H 可抑制大鼠心房纤维化及缝隙连接蛋白 43 重构。

关键词:U50488H;心房纤维化;Cx43 重构;κ 阿片受体

中图分类号:R-33;R54 文献标识码:A 文章编号:1673-6273(2020)18-1824-04

Effects of Selective κ-opioid Receptor Agonist U50488H on Atrial Fibrosis and Connexin43 Remodeling in Rats*

BAO Hong-gang¹, SU Fang-ju², XU Zhi-yong¹, ZHU Li-qiang¹, XUE Li¹, YANG Hai-qing^{1Δ}

(1 Department of Cardiology, The central theater air force hospital, Datong, Shanxi, 037000, China;

2 Department of Cardiology, 940 Hospital of PLA, Lanzhou, Gansu, 730000, China)

ABSTRACT Objective: To observe the effects of selective κ-opioid receptor agonist U50488H on atrial fibrosis and connexin43 remodeling in rats induced by Isoprenaline(ISO). **Methods:** Forty SPF male wistar rats were randomly divided into four groups($n=10$): control group, ISO(5 mg/[kg·d]) group (ISO group), ISO[5 mg/(kg·d)]+U50488H [1.5 mg/(kg·d)] group (U50488H group), ISO[5 mg/(kg·d)]+Nor-BNI [2 mg/(kg·d)]+U50488H [1.5 mg/(kg·d)]group (Nor-BNI group). Each group was given corresponding reagents once a day. The rats were killed after 7 days. H-E staining was used to observe myocardial fibrosis and Masson staining was used to calculate collagen volume fraction; Immunohistochemical method was used to observe the distribution of Cx43, Western blot was used to detect the expression of Cx43. **Results:** ① The results of H-E and Masson staining showed that there was no significant atrial fibrosis in the control group and there was significant fibrosis in the ISO group, while the degree of atrial fibrosis in the U50488H group was weaker than that in the ISO group ($P<0.01$), and its effect could be inhibited by Nor BNI. ② Compared with the control group, the Content of Cx43 obviously reduced($P<0.01$) and distribution disordered very much in ISO group, while the content of Cx43 in U50488H group was not obvious changed ($P<0.01$) and the distribution is regularly, the effect of U50488H can be inhibited by Nor-BNI. **Conclusion:** The selective agonist U50488H of κ opioid receptor can inhibit the atrial fibrosis and the connexin 43 remodeling in rats.

Key words: U50488H; atrial fibrosis; Cx43; κ-opioid receptor

Chinese Library Classification(CLC): R-33; R54 **Document code:** A

Article ID: 1673-6273(2020)10-1824-04

前言

心肌重构是心力衰竭、心律失常的重要环节,多个研究表明心房纤维化与缝隙连接蛋白 43(connexin43 Cx43) 重构是心

肌重构的重要表现形式并与室性心律失常和房颤的发生、发展有着密切的联系^[1-4]。已有研究表明心房纤维化在房颤的维持与发生中充当重要角色,抑制心房纤维化可减少房颤的发生^[5,6]。Cx43 是心肌细胞电耦联及化学耦联的基础,正常心肌细胞中

* 基金项目:全军 2017 年后勤科研面上项目(CWH17L004)

作者简介:鲍宏刚(1982-),男,主治医师,硕士研究生,研究方向:冠心病、心律失常的基础与临床,E-mail: baohonggang@163.com

Δ 通讯作者:杨海青(1978-),女,副主任技师,博士研究生,主要研究方向:心血管内科、医院管理,E-mail: 18931258016@189.cn

(收稿日期:2019-11-26 接受日期:2019-12-22)

Cx43 呈簇状分布在闰盘,主要呈端对端分布^[7]。其在心肌的数量、空间分布均可影响缝隙间电荷耦联和代谢耦联的功能,导致心律失常的发生。研究表明^[8,9],心肌缺血情况下可引起 Cx43 重构,主要表现为 Cx43 数量的减少及分布的紊乱,导致这种情况的机制目前仍不完全明确,心肌梗死后神经重构,可能是 Cx43 重构的主要机制之一^[10,11]。研究表明^[12-14]心脏交感神经系统、 β 受体系统在房颤的发生过程中起到了重要作用,已有研究证实^[15,16] κ 阿片受体选择性激动剂 U50488H 对交感神经系统、 β 受体系统具有广泛的抑制作用,并且可以通过调节心室肌细胞 Cx43 的表达而发挥抗缺血/再灌注性心律失常的作用^[17],尚有研究^[18]发现 U50488H 对心肌细胞的生长具有负性调控作用,可以抑制心肌纤维化。但其是否可抑制 β 受体激动剂-盐酸异丙肾上腺素所致的大鼠心房纤维化及缝隙连接蛋白重构,尚未见相关报道。故本研究参考 Zhang 等^[19]方法采用皮下多点注射大剂量盐酸异丙肾上腺素(isoprenaline ISO)诱导产生大鼠心房纤维化模型,观察 κ 阿片受体选择性激动剂 U50488H 对大鼠心房纤维化及缝隙连接蛋白 43 重构的影响。

1 材料与方法

1.1 材料

SPF 级雄性 wistar 大鼠,体重(180 $\pm$ 20)g,由甘肃省中医院实验动物中心提供。U50488H、Nor-BNI 购自美国 Sigma 公司,盐酸异丙肾上腺素购自上海禾丰制药有限公司,羊抗兔生物素标记性二抗、DAB 染色试剂盒均购自武汉博士德生物工程有限公司,抗体稀释液(上海碧云天生物技术有限公司),兔抗鼠 connexin 43 抗体、GAPDH (美国, Santa Cruz),蛋白质预染分子量 Marker(立陶宛, Fermentas)。

1.2 实验分组及动物模型的建立

40 只 SPF 级雄性 wistar 大鼠,体重(180 $\pm$ 20)g,按随机数字表法随机等分为 4 组:对照组、盐酸异丙肾上腺素(isoprenaline ISO)[5 mg/(kg·d)](ISO 组)、ISO[5 mg/(kg·d)]+U50488H [1.5 mg/(kg·d)]组(U50488H 组)、ISO[5 mg/(kg·d)]+Nor-BNI(κ 阿片受体阻断剂)[2 mg/(kg·d)]+U50488H [1.5 mg/(kg·d)]组(Nor-BNI 组)。ISO 组、U50488H 组、Nor-BNI 组大鼠按 5 mg/kg 体质量腹部皮下多点注射 ISO(购自上海禾丰制药有限公司),注射时用左手拇指及食指轻轻捏起小鼠腹部的皮肤,右手持注射器钝角角度将针头刺入,刺入后把针头轻轻向左右摆动,易摆动则表示已刺入皮下,再轻轻抽吸,若无回血,可缓慢地将药液注入皮下。出针后应按压针刺部位,防止药物外漏和促进药物吸收。1 次/d;U50488H 组于 ISO 注射前 20 min 按 1.5 mg/kg 体质量给予 U50488H 尾静脉注射,小鼠尾静脉在左右两侧和背侧各 1 根,操作时,先将动物固定在暴露尾部的固定器内,用 75%酒精棉球反复擦拭使血管扩张,用左手拇指和食指捏住鼠尾两侧,注射时针头尽量采取与尾部平行的角度($<30^\circ$)进针。开始注射时宜少量缓注,如无阻力,表示针头已进入静脉,如有白色皮丘出现,说明未刺入血管,应向小鼠身体方向移动,重新注射。1 次/d;Nor-BNI 组在给予 U50488H 溶液前 1 小时,按 2 mg/kg 体质量给予 Nor-BNI 腹腔注射,注射时用左手拇指和食指捏住两耳及头皮,无名指和小指捏住尾巴。腹部向上,头呈低位把小鼠控制在手掌间,腹部用酒精棉球擦拭消毒,

然后将针头由下腹部腹中线两侧朝头方向刺入腹腔,回抽无肠液、尿液后,缓缓推入药液。撤针时先按照注射方向向后退然后再水平方向撤出,改变通路,减少液体溢出。1 次/d;按以上给药方法连续给药 7 天。对照组大鼠分别在相应时间内皮下注射、尾静脉注射、腹腔注射与 ISO 组、U50488H 组、Nor-BNI 组等量的生理盐水。

1.3 取材及标本保存

各组大鼠按上述方案连续给药至第 7 d 时处死。沿心脏长轴剪开大鼠心脏,暴露心腔并取部分心房组织置于中性甲醛液中固定 24 小时,经石蜡包埋后,连续切片 3 张,每张厚 3 μ m,2 张分别用于 H-E 染色和 Masson 染色,1 张用免疫组化法观察心肌组织中 Cx43 表达及分布。剩余心房组织取出后立即放入冻存管中并置 -80 $^\circ$ C 冰箱中冷冻保存,用于 western blot 法检测心房肌组织中 Cx43 的含量。

1.4 大鼠心肌组织病理改变及 CVF 计算

心肌石蜡组织切片常规 HE、Masson 染色,光镜下观察心房肌纤维化及心肌细胞排列情况并摄片,Masson 染色的切片每张选取 4 个不重叠无血管视野($\times 400$)拍照,运用 Image-Pro plus 5.0 图像扫描软件进行图像分析并计算心肌 CVF。CVF(%)= 胶原面积/全视野面积 $\times 100\%$ 。

1.5 免疫组化 SP 法观察大鼠心肌组织中 Cx43 的表达及分布

将心肌组织切片置于 68 $^\circ$ C 烤箱中烤 60 min 后行免疫组化染色,镜下观察 Cx43 分布情况,每张切片中各取 4 个非重叠无血管视野($\times 400$),利用 Image-Proplus 5.0 图像扫描软件进行图像分析,测定每个视野下阳性物质的平均光密度值(mean density),mean density= 累积光密度值(IOD SUM)/面积(area)。

1.6 Western blot 测定心肌组织中 Cx43 的蛋白表达

每只大鼠取心肌组织 100 mg 加入蛋白裂解液裂解,低温研磨,4 $^\circ$ C 离心 1 min,离心力为 10000($\times g$),电泳:Tris-Glycine (pH8.0)缓冲液,恒压 80V,1.5-2 hrs。预先备好与胶同样大小的滤纸和 NC 膜。NC 膜先在电转缓冲液中浸泡 30 min;滤纸也在电转缓冲液中浸泡润湿。放置好滤纸、胶、NC 膜,恒压 20V,电转 1.5 hrs。将膜取下,剪角后在 5%脱脂奶粉封闭液(PBST)中室温下缓慢摇动 1.5 hrs;将 Cx43 抗体用 5%脱脂奶粉/PBST 稀释至 1:400 并过夜,将内参---鼠抗 GAPDH 单克隆抗体用 5%脱脂奶粉/PBST 稀释至 1:10000,4 $^\circ$ C 过夜;PBST 洗膜 10 min $\times$ 3 次;辣根过氧化物酶标记羊抗兔二抗用 5%脱脂奶粉/PBST 稀释至 1:2000,内参---羊抗鼠二抗用 5%脱脂奶粉/PBST 稀释至 1:2000,室温孵育 1h;PBST 洗膜 15 min $\times$ 3 次。把膜放于 WEST PICO 两分钟,压片,显影,检测 Cx43 蛋白条带。凝胶成像系统拍照。并测定目的蛋白与内参的比值即灰度比值(D)。

1.7 统计分析

所有数据以 $\bar{x} \pm s$ 表示,采用 SPSS13.0 软件进行统计分析,单因素方差分析用于组间比较,LSD 法用于两两比较, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 H-E 染色

在整个实验过程中,各组实验动物均未发生死亡,期间大

鼠体重无明显减轻。H-E 染色结果(图 1),图中可见对照组中大鼠心肌纤维清晰,排列规则,无明显纤维化;而 ISO 组、NOR-BNI 组中大鼠心肌纤维排列紊乱、部分纤维断裂、扭曲呈波

浪状,细胞外间隙增宽,纤维化程度明显;而 U50488H 组较 ISO 组纤维化程度明显减轻。

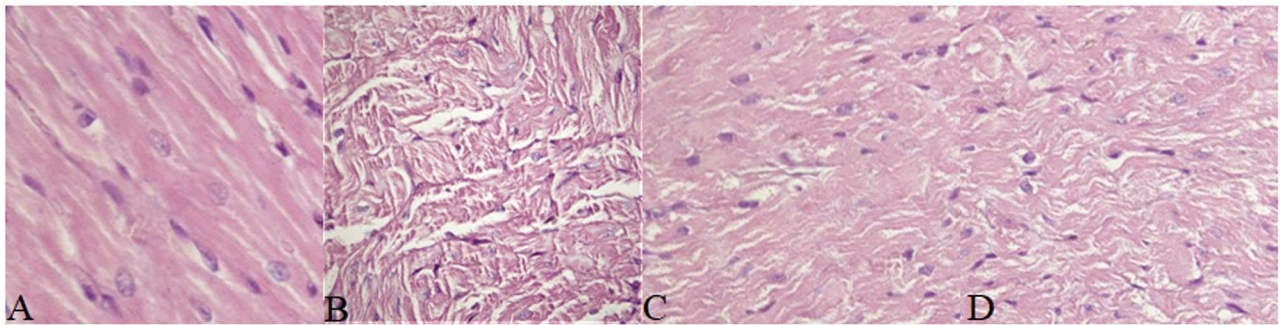


图 1 各组大鼠心房肌纤维化 HE 染色结果($\times 400$)

Fig.1 Atrial fibrosis HE staining in each group ($\times 400$)

注: A: 对照组;B: ISO 组;C: U50488H 组;D: NOR-BNI 组。图中心肌组织的细胞核被染成蓝色,细胞质、肌纤维、胶原纤维和红细胞均呈红色。可见对照组中大鼠心肌纤维清晰,排列规则,无明显纤维化;而 ISO 组、NOR-BNI 组中大鼠心肌纤维排列紊乱、部分纤维断裂、扭曲呈波浪状,细胞外间隙增宽,纤维化程度明显;而 U50488H 组较 ISO 组纤维化程度明显减轻。

Note: A: control group; B: ISO group; C: U50488H group; D: NOR-BNI group. The nucleus of the central muscle tissue was stained blue, and the cytoplasm, muscle fiber, collagen fiber and red cells were all red. It can be seen that the myocardial fibers in the control group are clear, arranged regularly, and without obvious fibrosis; while in the ISO group and NOR-BNI group, the arrangement of muscle fibers is disordered, some fibers are broken and twisted in waves, the extracellular space is widened, and the degree of fibrosis is obvious; while in the U50488H group, the degree of fibrosis is significantly less than that in the ISO group.

2.2 Masson 染色和 CVF

Masson 染色结果(图 2),CVF 结果由低到高依次为:对照组 $[(9.08 \pm 2.18)\%]$ 、U50488H 组 $[(11.91 \pm 2.53)\%]$ 、NOR-BNI 组 $[(40.57 \pm 7.03)\%]$ 、ISO 组 $[(41.38 \pm 6.90)\%]$ 。与对照相比,

NOR-BNI 组和 ISO 组出现明显的心房纤维化 (P 均 < 0.01),而 U50488H 组与对照组相比差异无统计学意义 (P 均 > 0.05),心房纤维化程度较 NOR-BNI 组和 ISO 组明显减轻 (P 均 < 0.01)。

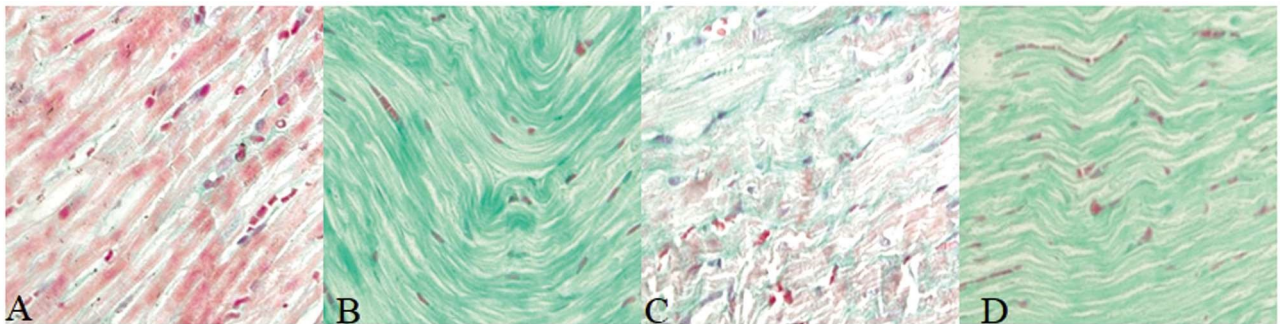


图 2 各组大鼠心房肌间质纤维化 Masson 染色结果($\times 400$)

Fig.2 Masson staining results of atrial interstitial fibrosis in each group ($\times 400$)

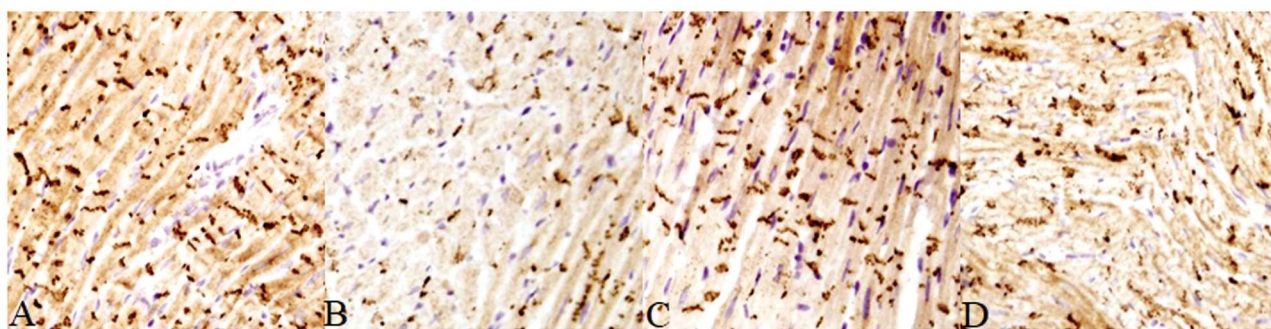
注: A: 对照组;B: ISO 组;C: U50488H 组;D: NOR-BNI 组。镜下绿色部分代表心肌间质胶原成分,细胞质、心肌纤维和红细胞被染成深浅不一的红色,细胞核则被染成蓝色。可见与对照组相比,NOR-BNI 组和 ISO 组出现明显的心房纤维化 (P 均 < 0.01),而 U50488H 组与对照组相比差异无统计学意义 (P 均 > 0.05),心房纤维化程度较 NOR-BNI 组和 ISO 组明显减轻 (P 均 < 0.01)。

Note: A: control group; B: ISO group; C: U50488H group; D: NOR-BNI group. Under the microscope, the green part represents the collagen composition of myocardial interstitium, and the cytoplasm, myocardial fibers and red cells are stained different shades of red, while the nucleus is stained blue. Compared with the control group, there was significant atrial fibrosis in NOR-BNI group and ISO group ($P < 0.01$), but there was no significant difference between U50488H group and the control group ($P > 0.05$), and the degree of atrial fibrosis was significantly reduced compared with nor-bni group and ISO group ($P < 0.01$).

2.3 免疫组化观察心房肌 Cx43 的分布及含量

正常心肌细胞的 Cx43 线性规律分布于心肌细胞闰盘处,免疫组化染色阳性呈棕黄色。免疫组化法染色(图 3)及半定量分析结果显示:对照组中 Cx43 多分布在与心肌纤维垂直的端端连接部位,即心肌的闰盘处,呈线性分布。ISO 组、NOR-BNI 组中 Cx43 分布无规律性,心肌侧面分布即侧侧连接相对增多,而

在 U50488H 组中 Cx43 的分布则趋于正常。Cx43 含量在 ISO 组 (0.196 ± 0.041) 、Nor-BNI 组 (0.207 ± 0.044) 较对照组 (0.366 ± 0.046) 减少 (P 均 < 0.01),U50488H 组中 Cx43 含量 (0.359 ± 0.049) 减少程度较 ISO 组、Nor-BNI 组减轻 ($P < 0.01$),与对照组相比无明显差异 ($P > 0.05$)。

图 3: 各组大鼠心房肌 Cx43 免疫组化染色结果($\times 400$)Fig.3: Cx43 immunohistochemical staining results of atrium in each group ($\times 400$)

注: A: 对照组; B: ISO 组; C: U50488H 组; D: NOR-BNI 组。正常心肌细胞的 Cx43 分布于心房肌细胞的闰盘处, 即与心肌纤维走向垂直, 免疫组化染色阳性呈棕黄色。图中可见对照组中 Cx43 多分布在与心肌纤维垂直的端端连接部位, 即心肌的闰盘处, 呈线性分布。而 ISO 组、Nor-BNI 组中 Cx43 分布无规律性, 心肌侧面分布即侧侧连接相对增多, 而在 U50488H 组中 Cx43 的分布则趋于正常。Cx43 含量在 ISO 组、Nor-BNI 组较对照组减少($P < 0.01$), U50488H 组中 Cx43 含量减少程度较 ISO 组、Nor-BNI 组减弱($P < 0.01$), 与对照组相比无明显差异($P > 0.05$)。

Note: A: control group; B: ISO group; C: U50488H group; D: NOR-BNI group. Cx43 of normal cardiomyocytes was distributed in intercalated disc of atrial myocytes, it was perpendicular to the direction of myocardial fiber, and the positive immunohistochemical staining was brownish yellow. In the figure, it can be seen that in the control group, most of the Cx43 were distributed in the end connection area perpendicular to the myocardial fiber, the moist disk of the myocardium, showing a linear distribution. In ISO group and NOR-BNI group, the distribution of Cx43 was irregular, and the distribution of myocardial lateral connection was relatively increased, while in U50488H group, the distribution of Cx43 tended to be normal. The content of Cx43 in the ISO group and nor-bni group was lower than that in the control group ($P < 0.01$). The content of Cx43 in the U50488H group was lower than that in the ISO group and nor-bni group ($P < 0.01$). There was no significant difference between the two groups ($P > 0.05$).

2.4 Western blot 法检测心房肌 Cx43 的含量

检测结果显示: 对照组中 Cx43 含量与 U50488H 组比较差异无统计学意义($P > 0.05$), 而 ISO 组、Nor-BNI 组中 Cx43 含

量较以上两组明显减少(P 均 < 0.01), 且 ISO 组与 or-BNI 组中 Cx43 含量差异无统计学意义($P > 0.05$), 此检测结果与免疫组化检测结果相符。

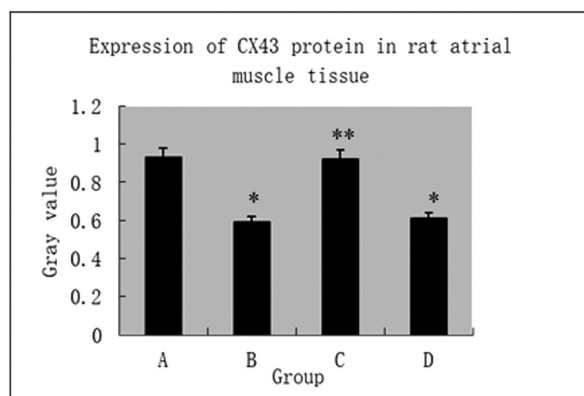
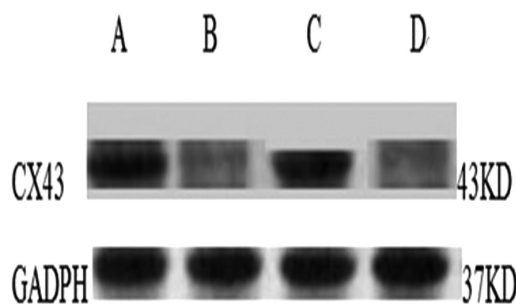


图 4 Western blot 法检测心房肌 Cx43 的含量

Fig.4 Western blot for the detection of Cx43 content in atrium

注: A: 对照组; B: ISO 组; C: U50488H 组; D: NOR-BNI 组。与对照组比较, $*P < 0.01$; 与 ISO 组相比较, $**P < 0.01$ 。

Note: A: control group; B: ISO group; C: U50488H group; D: nor-bni group. Compared with the control group, $*P < 0.01$; compared with the ISO group, $**P < 0.01$.

3 讨论

心肌纤维化与多种心血管疾病发生发展密切相关, 纤维化的心肌可使心肌顺应性降低, 心肌收缩力减轻, 不仅影响心脏的收缩及舒张功能^[20], 而且纤维化的心肌易致电兴奋传导的不均匀, 易于折返形成, 与心律失常的发生密切相关。研究^[21-23]表明心房纤维化与房颤的发生关系密切, 是房颤发生与维持的基础之一。

Cx43 是心肌闰盘处的特殊结构, 作为相邻心肌细胞间电

和化学信号传递的通道, 在促使动作电位的协同扩布、实现心肌细胞运动同步化中发挥重要作用^[24,25]。但在一些情况下 Cx43 可发生重构, Cx43 重构后容易引发功能紊乱, 导致心律失常。Cx43 作为心房中主要的连接蛋白, 大部分呈线状分布于闰盘部位, 心肌细胞膜侧面分布极少。Cx43 表达量减少、非均匀化及侧面化是 Cx43 重构的主要表现形式, 是心房结构重构的重要因素。Cx43 表达量的减少及非均匀化可改变电传导的同向性, 使电传导速率降低, 且易形成折返, 造成心律失常。而 GJ 的侧面化, 可使 Cx43 形成的半通道增多, 可导致 Na^+ 内流和

ATP 外流,引起延迟后去极化^[26,27],病理条件下心肌 Cx43 的这些重构,是构成心律失常的基础。

研究^[28]发现 Cx 基因治疗可预防 AF 的发生。而且有研究指出心房纤维化与缝隙连接蛋白重构是房颤时心房结构重构的重要表现形式,在房颤的发生与维持中起到重要作用^[29,30],因此抑制心房纤维化和 Cx43 的重构对于房颤的防治具有重要意义。研究证实^[16]κ 阿片受体选择性激动剂 U50488H 可以通过抑制 β 受体系统来调节心室肌细胞 Cx43 的表达而发挥抗缺血 / 再灌注性心律失常的作用并^[17]对心肌细胞的生长具有负性调控作用。进一步的研究^[31]发现持续性房颤患者 κ 阿片受体 mRNA 表达较正常人降低,表明 κ 阿片受体对房颤具有保护作用,但 κ 阿片受体选择性激动剂 U50488H 是否可抑制 β 受体激动剂 - 盐酸异丙肾上腺素所致的大鼠心房纤维化及缝隙连接蛋白重构,尚未见相关报道。

本实验中大鼠大剂量皮下注射 ISO7d 后发现与对照组相比,ISO 组心房纤维化明显,Cx43 表达量减少、侧侧连接相对增多,这一结果与张卫泽、鲍宏刚^[28,29]的研究结论相符,表明通过皮下注射 ISO 可诱导大鼠心肌纤维化及缝隙连接蛋白 43 的重构。而 U50488H 组心肌纤维化和 Cx43 重构较 ISO 组明显减轻,提示 U50488H 对 ISO 诱发的心房纤维化和 Cx43 重构具有保护作用;虽然研究方法不同,但该结果与王伟光、杨彦玲^[17,18]等研究得出的结果相一致。对于 Cx43 重构具体表现,本研究 and 既往研究^[8,9]均得出 Cx43 数量的减少及分布的紊乱是 Cx43 重构的重要表现形式。进一步研究发现 NOR-BNI 组使用 κ 阿片受体抑制剂后心肌纤维化程度和 Cx43 重构明显,与 ISO 组比较无明显差别,再次表明 U50488H 对 ISO 诱发的心房纤维化和 Cx 重构的保护作用主要是通过激活 κ 阿片受体来实现的,一旦使用了 κ 阿片受体抑制剂,这种保护作用也即消失。

综上所述,U50488H 可通过激活 κ 阿片受体而起到抑制 ISO 引起的大鼠心房纤维化和 Cx43 重构的作用,这一作用可能与 κ 阿片受体激活后抑制 β 受体系统有关,但具体机制尚待进一步探讨,这一发现为房颤的防治提供了新的思路。

参考文献(References)

- [1] Lv X, Li J, Hu Y, Wang S, et al. Overexpression of miR-27b-3p Targeting Wnt3a Regulates the Signaling Pathway of Wnt/β -Catenin and Attenuates Atrial Fibrosis in Rats With Atrial Fibrillation[J]. Oxid Med Cell Longev, 2019, 57(03): 764
- [2] Bao Hong-gang, Zhang Wei-ze, Li Tao, et al. Effects of Ala-Gln on Myocardial Fibrosis and Connexin43 Remodeling in Experimental Rats' Model[J]. Chinese Circulation Journal, 2014, 29(12): 1024-1028
- [3] Osbourne A, Calway T, Broman M, et al. Downregulation of connexin43 by microRNA-130a in cardiomyocytes results in cardiac arrhythmias[J]. J Mol Cell Cardiol, 2014, 74: 53-63
- [4] Luo B, Yan Y, Zeng Z et al. Connexin 43 reduces susceptibility to sympathetic atrial fibrillation[J]. Int J Mol Med, 2018, 42(2):1125-1133
- [5] YUANCH, LIX X, Cheng QJ, et al. Mir-30 regulates the atrial fibrillation-induced myocardial fibrosis by targeting snail[J]. Int J Clin Exp Pathol, 2015, 8(12): 15527-15536
- [6] Stanley Nattel. Molecular and Cellular Mechanisms of Atrial Fibrosis in Atrial Fibrillation [J]. JACC Clin Electrophysiol, 2017, 3 (5): 425-435

- [7] Picoli C, Nouvel V, Aubry F, et al. Human connexin channel specificity of classical and new gap junction inhibitors [J]. J Biomol Screen, 2012, 17: 1339-1347
- [8] Rainer Schulz, Philipp Maximilian Gorge, Anikó Görbe, et al. Connexin 43 Is an Emerging Therapeutic Target in Ischemia/Reperfusion Injury, Cardioprotection and Neuroprotection[J]. Pharmacol Ther, 2015, 153: 90-106
- [9] Peng Zhang, Jin Xu, Wei Hu, et al. Effects of Pinocembrin Pretreatment on Connexin 43 (Cx43) Protein Expression After Rat Myocardial Ischemia-Reperfusion and Cardiac Arrhythmia [J]. Med Sci Monit, 2018, 24: 5008-5014
- [10] Wajid Hussain, Pravina M Patel, Rasheda A Chowdhury, et al. The Renin-Angiotensin System Mediates the Effects of Stretch on Conduction Velocity, connexin43 Expression, and Redistribution in Intact Ventricle[J]. J Cardiovasc Electrophysiol, 2010, 21(11): 1276-1283
- [11] Salameh A, Krautblatter S, Baessler S, et al. Signal transduction and transcriptional control of cardiac connexin43 up-regulation after alpha 1-adrenoceptor stimulation [J]. J Pharmacol Exp Ther, 2008, 326: 315-322
- [12] Ahsan A Khan, Gregory Y H Lip, Alena Shantsila, et al. Heart Rate Variability in Atrial Fibrillation: The Balance Between Sympathetic and Parasympathetic Nervous System [J]. Eur J Clin Invest, 2019, 49 (11): e13174
- [13] Peng-Sheng Chen, Lan S Chen, Michael C Fishbein, et al. Role of the Autonomic Nervous System in Atrial Fibrillation: Pathophysiology and Therapy[J]. Circ Res Actions, 2014, 114(9): 1500-1515
- [14] 吴敏,汤宝鹏.自主神经系统与心房颤动研究新进展[J].中国心脏起搏与心电生理杂志, 2017, 31(1): 59-60
- [15] Shan D, Wang H, Su Y, et al. Kappa-opioid receptor stimulation inhibits cardiac hypertrophy induced by beta1-adrenoceptor stimulation in the rat[J]. Eur J Pharmacol, 2007, 555(2-3): 100-105
- [16] Meili Lu, Hongxin Wang, Yuhong Yang, et al. The Function of Calcineurin and ERK1/2 Signal in the Antihypertrophic Effects of Kappa-Opioid Receptor Stimulation on Myocardial Hypertrophy Induced by Isoprenaline [J]. Pharmazie, 2012, 67(2): 182-186
- [17] 王伟光,张权宇,曹钰琨,等.κ 阿片受体可通过抑制 β 肾上腺素受体进而调节心肌细胞 Cx43 发挥抗缺血 / 再灌注性心律失常[J].中国药理学通报, 2010, 26(4): 471-476
- [18] 杨彦玲,王洪新,杨育红.κ 阿片受体激活对培养心肌细胞生长抑制的影响[J].中国应用生理学杂志, 2002, 18(4): 358-361
- [19] Zhang YG, Li YG, Liu BG, et al. Urotensin II accelerates cardiac fibrosis and hypertrophy of rats induced by isoproterenol[J]. Acta Pharmacol Sin, 2007, 28(1): 36-43
- [20] Arantxa González, Erik B Schelbert, Javier Díez. Myocardial Interstitial Fibrosis in Heart Failure: Biological and Translational Perspectives[J]. J Am Coll Cardiol, 2018, 71(15): 1696-1706
- [21] Karagueuzian HS, Nguyen TP, Qu Z, Weiss JN. Oxidative stress, fibrosis, and early afterdepolarization-mediated cardiac arrhythmias[J]. Front Physiol, 2013, 4: 1-19
- [22] Tan AY, Zimetbaum P. Atrial fibrillation and atrial fibrosis[J]. J Cardiovasc Pharmacol, 2011, 57(6): 625-629

(下转第 1888 页)

(上接第 1828 页)

- fever and rheumatic heart disease [J]. The Lancet, 2017, 390(10091): 212-213
- [13] Saxena A, Desai A, Narvencar K, et al. Echocardiographic prevalence of rheumatic heart disease in Indian school children using World Heart Federation criteria-A multi site extension of RHEUMATIC study (the e-RHEUMATIC study)[J]. Int J Cardiol, 2017, 249(184): 438-442
- [14] Tri H HQ, Vinh PN. Progression of Tricuspid Regurgitation after Mitral Valve Replacement for Rheumatic Heart Disease [J]. J Heart Valve Dis, 2017, 26(3): 290-294
- [15] Beaton A, Aliku T, Dewyer A, et al. Latent Rheumatic Heart Disease: Identifying the Children at Highest Risk of Unfavorable Outcome[J]. Circulation, 2017, 136(23): 2233-2244
- [16] Sikder S, Williams NL, Sorenson AE, et al. Group G streptococcus induces an autoimmune IL-17A/IFN- γ mediated carditis in the Lewis rat model of Rheumatic Heart Disease [J]. J Infect Dis, 2017, 218(2): 324-335
- [17] Ge Y, Liu C, Niu Y, et al. Associations between ambient temperature and daily hospital admissions for rheumatic heart disease in Shanghai, China[J]. Int J Biometeorol, 2018, 62(12): 2189-2195
- [18] French KA, Poppas A. Rheumatic Heart Disease in Pregnancy[J]. Circulation, 2018, 137(8): 817-819
- [19] Mellinger JD, Williams RG, Sanfey H, et al. Teaching and assessing operative skills: From theory to practice[J]. Curr Probl Surg, 2017, 54(2): 44-81
- [20] Lahewala S, Arora S, Patel P, et al. Atrial fibrillation: Utility of CHADS 2, and CHA 2 DS 2 -VASc scores as predictors of readmission, mortality and resource utilization [J]. Int J Cardiol, 2017, 245(90): 162-167
- [21] Chaudhary P, Kumar R, Sagar V, et al. Assessment of Cpa, Scl1 and Scl2 in clinical group A streptococcus isolates and patients from north India: an evaluation of the host pathogen interaction[J]. Res Microbiol, 2018, 169(1): 11-19
- [22] Hensel M, GrDel L, Kutz A, et al. Peripheral monocytosis as a predictive factor for adverse outcome in the emergency department[J]. Med, 2017, 96(28): e7404
- [23] Poomarimuthu M, Elango S, Solomon PR, et al. Association of IL17 and IL23R gene polymorphisms with rheumatic heart disease in South Indian population[J]. Immunol Invest, 2018, 47(7): 754-764
- [24] Toor D, Sharma N. T cell subsets: an integral component in pathogenesis of rheumatic heart disease [J]. Immunol Res, 2017, 66(9480): 1-13
- [25] Conde mi F, Rossi G, Lupiz M, et al. Screening of asymptomatic rheumatic heart disease among refugee/migrant children and youths in Italy[J]. Pediatr Rheumatol Online J, 2019, 17(1): 22-23
- [26] Gurney JK, Chong A, Culliford-Semmens N, et al. High levels of rheumatic fever and sore throat awareness among a high-risk population screened for rheumatic heart disease [J]. N Z Med J, 2017, 130(1450): 107-110
- [27] Roberts K, Cannon J, Atkinson D, et al. Echocardiographic Screening for Rheumatic Heart Disease in Indigenous Australian Children: A Cost-Utility Analysis[J]. J Am Heart Assoc, 2017, 6(3): e004515
- [28] Okello E, Longenecker CT, Beaton A, et al. Rheumatic heart disease in Uganda: predictors of morbidity and mortality one year after presentation[J]. BMC Cardiovasc Disord, 2017, 17(1): 20-35
- [29] Laudari S, Subramanyam G. A study of spectrum of rheumatic heart disease in a tertiary care hospital in Central Nepal [J]. Int J Cardiol Heart Vasc, 2017, 15(7): 26-30
- [30] Zühlke LJ, Beaton A, Engel ME, et al. Group A Streptococcus, Acute Rheumatic Fever and Rheumatic Heart Disease: Epidemiology and Clinical Considerations[J]. Curr Treat Options Cardiovasc Med, 2017, 19(2): 15-48
- [23] Kalman JM, Kumar S, Sanders P. Markers of collagen synthesis, atrial fibrosis, and the mechanisms underlying atrial fibrillation [J]. J Am Coll Cardiol, 2012, 60(18): 1807-1808
- [24] Joell L Solan, Paul D Lampe. Spatio-temporal Regulation of connexin43 Phosphorylation and Gap Junction Dynamics [J]. Biochim Biophys Acta Biomembr, 2018, 1860(1): 83-90
- [25] Saffitz JE, Schuessler RB, Yamada KA. Mechanisms of remodeling of gap junction distributions and the development of anatomic substrates of arrhythmias[J]. Cardiovasc Res, 1999, 42: 309-317
- [26] 余志斌, 圣娟娟. 心肌细胞缝隙连接重塑与心律失常[J]. 生理学报, 2011, 63: 586-592
- [27] Saffitz JE, Schuessler RB, Yamada KA. Mechanisms of remodeling of gap junction distributions and the development of anatomic substrates of arrhythmias[J]. Cardiovasc Res, 1999, 42: 309-317
- [28] Igarashi T, Finet JE, Takeuchi A, et al. Connexin gene transfer preserves conduction velocity and prevents atrial fibrillation [J]. Circulation, 2012, 125(2): 216-25
- [29] 鲍宏刚, 张卫泽, 马凌, 等. 谷氨酰胺诱导热休克蛋白 70 高表达可抑制大鼠心房纤维化及缝隙连接蛋白 43 重构[J]. 中华心血管病杂志, 2013, 41(4): 320-326
- [30] 张卫泽, 王智刚, 陈永清, 等. 缬沙坦与 U0126 对大鼠心肌纤维化和缝隙连接蛋白 40 的影响[J]. 中华心血管病杂志, 2011, 39(12): 1129-1134
- [31] 张宪伟, 郑强荪, 胡晓燕, 等. 心房纤颤患者心房 κ 阿片肽受体表达的变化和意义[J]. 心血管康复医学杂志, 2007, 16(2): 123-125