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活化的乙醛脱氢酶2通过调节双孔钾离子通道TASK-1减轻 糖尿病大鼠心肌损伤

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[摘要] 目的: 观察激活乙醛脱氢酶2(aldehyde dehydrogenase 2, ALDH2)对糖尿病心肌损伤中双孔钾离子通道TASK-1的影响及其对糖尿病心肌损伤的保护作用。方法: 将雄性SD大鼠随机分为正常组(N组)、糖尿病4周组(DM4W组)、糖尿病8周组(DM8W组), 糖尿病8周组+低浓度乙醇干预组(DM8W+EtOH组)。采用腹腔单次注射链脲佐菌素(55 mg/kg)复制糖尿病大鼠模型。行心脏超声测定大鼠心功能, ELISA法检测心肌组织羟脯氨酸含量, HE染色观察心肌组织结构, PAS染色观察心肌组织阳性物质沉积情况, Western印迹检测心肌组织TASK-1蛋白表达情况, 膜片钳记录心室肌细胞复极30%和90%时的动作电位时程(APD₃₀, APD₉₀)和双孔钾离子通道TASK-1电流, 同时根据该钾通道对酸碱敏感的电生理特性判断是否为双孔钾离子通道TASK-1电流。结果: 与N组相比, DM4W组和DM8W组大鼠左室舒张末期内径(end-diastole left ventricular diameter, LVIDd)及左室收缩末期内径(end-systolic left ventricular diameter, LVIDs)、羟脯氨酸含量、TASK-1蛋白表达增加, 左室内径缩短率(left ventricular fractional shortening, LVFS)和射血分数(left ventricular ejection fraction, LVEF)均下降, APD₃₀和APD₉₀延长, TASK-1电流减少($P<0.01$); HE染色结果显示DM4W组和DM8W组大鼠心肌细胞及纤维排列紊乱, 心肌细胞肥大, 心肌间隙增宽; PAS染色显示DM4W组和DM8W组大鼠心肌组织阳性物质沉积增加。与DM4W组相比, DM8W组大鼠上述指标的变化更加明显($P<0.05$ 或 $P<0.01$)。与DM8W组相比, DM8W+EtOH组左室心功能指标LVIDd, LVIDs, LVFS, LVEF有所恢复, 羟脯氨酸含量和TASK-1蛋白表达减少, TASK-1电流增加, APD₃₀和APD₉₀缩短(均 $P<0.01$); HE染色显示心肌细胞损伤较前减轻, PAS染色显示大鼠心肌组织阳性物质沉积减少。结论: ALDH2被低浓度的乙醇激活后可减轻糖尿病所致的心肌损伤及纤维化, 其机制可能与其调节双孔钾离子通道TASK-1蛋白表达和TASK-1电流有关。

[关键词] 糖尿病; 心肌损伤; 双孔钾离子通道; TASK-1

Activation of aldehyde dehydrogenase 2 attenuates myocardial injury in diabetic rats by regulating two-pore potassium channel TASK-1

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ABSTRACT

Objective: To investigate the effect of activating aldehyde dehydrogenase 2 (ALDH2) on TASK-1 two-pore potassium channel in myocardial injury of diabetic rats.

Methods: Diabetic rats were induced by intraperitoneal injection of streptozotocin (55 mg/kg). The diabetic rats were divided into 4 groups: normal group, diabetes at 4th week (DM4W) group, diabetes at 8th week (DM8W) group, and diabetes at 8th week+low concentration of ethanol intervention (DM8W+EtOH) group. The cardiac function of rats was determined by cardiac ultrasonography. The content of hydroxyproline was detected by ELISA. The appearance of myocardial morphous and positive material were observed by HE and PAS staining. The protein expression of TASK-1 was detected by Western blot. Whole-cell patch clamp technique was used to record the action potential duration at 30% and 90% repolarization (APD_{30} , APD_{90}) and two-pore potassium channel TASK-1 current in rat ventricular myocytes. Meanwhile, according to the sensitive electrophysiological characteristics of the potassium channel to acid and base, whether it is two-pore potassium channel TASK-1 current can be determined.

Results: Compared with the N group, end-diastole left ventricular diameter (LVIDd), end-systolic left ventricular diameter (LVIDs), hydroxyproline content, TASK-1 protein expression increased, APD_{30} and APD_{90} extend, left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF), and TASK-1 current decreased (all $P < 0.01$) in the DM4W group and the DM8W group. HE staining showed that myocardial cell and fiber arrangement disorder, myocyte hypertrophy, myocardial widened and PAS staining reveals that positive material increased in the DM4W group and the DM8W group. Compared with the DM4W group, these changes are more obvious in DM8W rats ($P < 0.01$ or $P < 0.05$). Compared with the DM8W group, in the DM8W+EtOH group, the left ventricular function was restored, the hydroxyproline content and expression of TASK-1 protein were decreased, the TASK-1 current was increased, and APD_{30} and APD_{90} were shortened (all $P < 0.01$). HE staining showed that myocardial cell injury was ameliorate and PAS staining showed decreased deposition of positive substances in the DM8W+EtOH group.

Conclusion: Activation of aldehyde dehydrogenase 2 by low concentration of ethanol can reduce myocardial injury and fibrosis caused by diabetes, and its mechanism may be related to the changes of the two-pore potassium channel TASK-1.

KEY WORDS

diabetes mellitus; myocardial injury; two-pore potassium channel; TASK-1

高血糖引起的心血管并发症涉及心肌组织和血管的变化,糖尿病心肌病(diabetic cardiomyopathy, DCM)是与糖尿病有关的一类特殊心肌病。1型和2型糖尿病均可导致DCM,临床上可表现为心力衰竭、心律失常、心源性休克甚至猝死。目前,DCM的发病机制尚未阐明,治疗方案也比较有限^[1]。心肌纤维化在DCM的发展进程中扮演着重要的角色。心肌纤维化是各种心脏疾病的病因学特征和病理基础,它会引起心肌僵硬和心脏功能障碍,最终导致心力衰竭等不良的临床结果^[2-3]。但是,心肌纤维化可能是可逆的,因此被认为是潜在的治疗靶点和影响预后的因素^[4-5]。

双孔钾离子通道定位于细胞膜上,是一种对于

钾离子高选择性的蛋白,其参与多个生理和病理过程,包括维持胞内离子稳态、调节细胞的增殖和凋亡等。它可感知各种的刺激,如机械压力、吸入麻醉药、细胞外pH值或温度的变化,并通过调节膜电位来诱导生理反应,双孔钾离子通道的活动形成了背景钾离子电流,从而有助于形成静息膜电位^[6]。TASK-1是双孔钾离子通道家族的一员,可调节神经元、心肌细胞、癌细胞的增殖和凋亡,调节胰腺激素分泌^[7-8]。研究^[9-10]表明:过高的氧化应激水平是心肌重构重要的驱动因素,心肌梗死后发生的氧化应激参与心肌电重构,引起心肌钾离子通道异常。笔者前期的研究^[11]也观察到双孔钾离子通道TASK-1在糖尿病大鼠心肌损伤模型中的电流降低而蛋白表达

增加。但是,钾离子通道在糖尿病大鼠心室重构及心律失常中发挥怎样的作用,目前报道较少。

线粒体乙醛脱氢酶2(aldehyde dehydrogenase 2, ALDH2)是体内重要的醛类氧化酶,可以有效地调节醛类的代谢,ALDH2的心肌保护作用已经被证明^[12]。Tao等^[13]研究发现:ALDH2激活可以减弱4-羟基壬烯醛(4-HNE)诱导的血管平滑肌细胞的增殖和迁移,减轻氧化应激。ALDH2被激活后,可以减少人脐静脉内皮细胞中LPS诱导的NF- κ B p65磷酸化和核易位^[14]。然而,ALDH2对DCM中双孔钾离子通道的影响仍然未知,未来的研究需要确定ALDH2是否通过双孔钾离子通道TASK-1参与心肌纤维化相关的心肌重构。本实验通过构建糖尿病大鼠心肌损伤模型,应用ALDH2的非特异性激动剂低浓度乙醇干预分析其可能机制。

1 材料与方 法

1.1 材料

链脲佐菌素(streptozotocin, STZ)购自美国Sigma公司;ELISA检测试剂盒购自南京建成生物工程研究所;ECL试剂盒购自美国Millipore公司;兔抗大鼠TASK-1抗体购自英国Abcam公司;兔抗大鼠 β -actin抗体购自Proteintech中国公司(武汉);山羊抗兔抗体购自合肥Biosharp公司。

1.2 分组

将32只雄性SD大鼠(蚌埠医学院实验动物中心提供)随机分为4组。1)正常大鼠对照组(N组);2)糖尿病4周组(DM4W组),糖尿病大鼠造模成功后继续喂养4周;3)糖尿病8周组(DM8W组),糖尿病大鼠造模成功后继续喂养8周;4)糖尿病8周+低浓度乙醇干预组(DM8W+EtOH组),糖尿病大鼠先以2.5%的乙醇适应性喂养1周,再以5%的乙醇持续喂养至8周。剔除造模过程死亡6只和不合格大鼠2只,最终入组24只,每组6只。

1.3 DCM大鼠模型的制备

SD大鼠适应性喂养1周,禁食12 h,腹腔单次注射STZ(55 mg/kg)。注射72 h后由尾静脉采血测血糖,以血糖 ≥ 16.7 mmol/L认为糖尿病大鼠造模成功。以后每4周测1次血糖,剔除血糖 < 16.7 mmol/L的大鼠。4周形成稳定的高血糖,8周后DCM模型建立成功^[15]。

1.4 心脏超声测定大鼠心功能

大鼠模型建立成功后,用乙醚麻醉并固定大鼠,暴露心前区,对大鼠行心脏超声检查,测定

大鼠左室射血分数(left ventricular ejection fraction, LVEF)、左室短轴缩短率(left ventricular fractional shortening, LVFS)、左室收缩末期内径(end-diastole left ventricular diameter, LVIDd)、左室舒张末期内径(end-systolic left ventricular diameter, LVIDs);所有数据测量3次取平均值^[11]。

1.5 心肌组织羟脯氨酸浓度的测定

将大鼠用戊巴比妥(40~50 mg/kg)腹腔注射麻醉后处死,取心脏并分装,按照ELISA试剂盒说明书操作,并根据试剂盒所给计算公式计算羟脯氨酸含量。

1.6 HE和PAS染色

将新鲜的心脏心尖部分切成5 mm \times 5 mm \times 5 mm组织块,用4%的多聚甲醛固定,石蜡包埋,行HE和PAS染色,光镜下观察心肌结构的变化及心肌组织内阳性物质沉积情况。

1.7 Western印迹检测心肌组织TASK-1的蛋白表达

取0.1 g心肌组织,加入细胞裂解液制取匀浆,于4 $^{\circ}$ C下3 000 r/min离心3 min,离心后提取上层清液。按照BCA试剂盒说明书测定蛋白浓度。制备10% SDS-PAGE分离胶和5%浓缩胶进行蛋白分离电泳,每组蛋白上样量60 μ g,然后将蛋白恒流转至PVD F膜,用5%脱脂奶粉在室温下封闭条带2 h, TASK-1或 β -actin一抗于4 $^{\circ}$ C孵育条带过夜。次日用TBST洗涤4次,加入HRP标记二抗IgG孵育1 h, TBST洗涤4次后采用ECL发光法显影成像^[15]。

1.8 膜片钳实验

急性分离大鼠心室肌细胞,于腹腔注射戊巴比妥(40~50 mg/kg)麻醉大鼠,快速开胸获取大鼠离体心脏并悬挂于Langendorff装置。选用无钙台氏液循环逆行灌流,待离体心脏残留血液冲洗干净且颜色变淡后,应用心肌消化酶液循环灌流离体心脏(流速5 mL/min)15~20 min,酶解完成后获取左心室,迅速置于KB液(含0.5 mg/mL BSA)中。将获取的大鼠左心室组织剪碎并反复吹打数次后离心,除去上层清液,在KB液中温育35 min,梯度复钙。根据实验需要记录电流数值。TASK-1电流的记录和复极30%和90%时的动作电位时程(APD₃₀, APD₉₀)的测定:通过电流钳和电压钳分别记录细胞膜电位(Em)和电流值,同时在电流钳下记录大鼠心肌细胞动作电位,并观察组间差异;为消除不同面积细胞间的电流误差,采用电流密度(电流强度与膜电容的比值, pA/pF)比较不同实验组间电流^[11]。

1.9 统计学处理

应用SPSS 22.0统计学软件进行数据的统计分析, 数据以均数±标准差($\bar{x}\pm s$)表示。各组间采用单因素方差分析, 两两比较采用 q 检验, 以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 大鼠心功能的变化

与N组相比, DM4W组和DM8W组大鼠心脏的LVIDd和LVIDs明显增加, LVEF和LVFS明显降低(均 $P<0.01$); 在糖尿病不同病程中, DM8W组较DM4W组

大鼠心脏的LVIDd和LVIDs明显增加, LVEF和LVFS明显降低(均 $P<0.01$); 与DM8W组相比, DM8W+EtOH组大鼠心脏的LVIDd和LVIDs明显降低, LVEF和LVFS明显增加(均 $P<0.01$; 表1, 图1)。

2.2 大鼠心肌羟脯氨酸含量变化

与N组[(1.69±0.07) $\mu\text{g}/\text{mg}$]相比, DM4W组[(1.84±0.07) $\mu\text{g}/\text{mg}$]和DM8W组[(2.56±0.12) $\mu\text{g}/\text{mg}$]大鼠心肌羟脯氨酸含量明显增加($P<0.01$), 且DM8W组较DM4W组增加更明显($P<0.01$), DM8W+EtOH组[(2.15±0.02) $\mu\text{g}/\text{mg}$]含量较DM8W组降低($P<0.01$)。

表1 各组大鼠心功能指标的变化($n=6, \bar{x}\pm s$)

Table 1 Changes of index of cardiac function in rats of each group ($n=6, \bar{x}\pm s$)

| 组别 | LVIDd/mm | LVIDs/mm | LVEF/% | LVFS/% |
|------------|---------------|---------------|----------------|----------------|
| N组 | 7.58±0.16 | 3.00±0.16 | 84.37±0.87 | 55.04±1.24 |
| DM4W组 | 8.14±0.16** | 4.83±0.33** | 73.18±3.78** | 43.89±3.74** |
| DM8W组 | 8.93±0.15**†† | 5.60±0.14**†† | 62.08±2.58**†† | 34.84±2.28**†† |
| DM8W+EtOH组 | 7.69±0.17‡‡ | 4.15±0.20‡‡ | 79.39±1.02‡‡ | 49.54±1.68‡‡ |

与N组比较, ** $P<0.01$; 与DM4W组比较, †† $P<0.01$; 与DM8W组比较, ‡‡ $P<0.01$

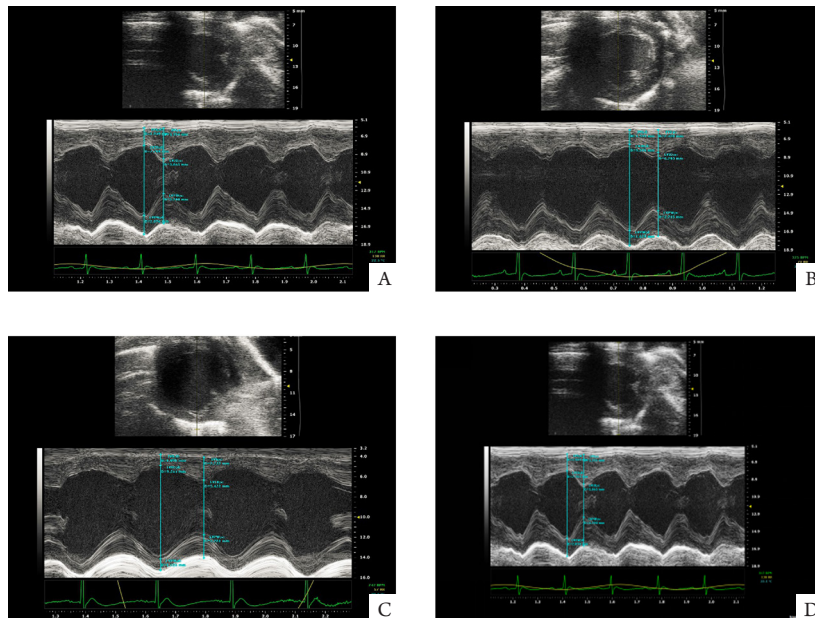


图1 心脏超声显示各组大鼠心功能的变化

Figure 1 Cardiac ultrasonography showing the changes of cardiac function in rats of each group

A: N group; B: DM4W group; C: DM8W group; D: DM8W+EtOH group

2.3 大鼠心肌HE染色结果

N组心肌细胞清晰, 排列规则, 纤维结构清楚, 心肌间隙正常, 未见炎性细胞浸润; DM4W组心肌细胞及纤维排列紊乱, 心肌细胞肥大, 心肌间隙

增宽; DM8W组心肌纤维出现断裂、溶解, 心肌细胞肥大、变性和坏死; 与DM8W组相比, DM8W+EtOH组心肌细胞上述病变减轻(图2)。

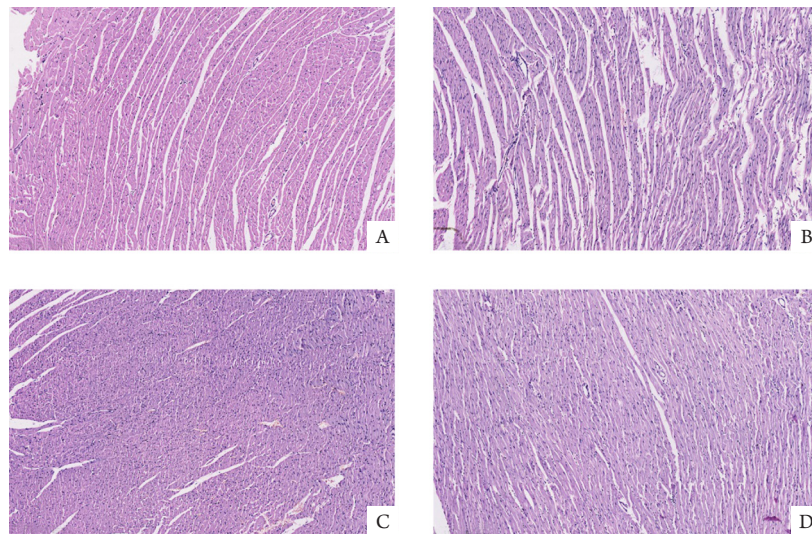


图2 HE染色观察心肌结构变化($\times 100$)

Figure 2 HE staining showing the changes of myocardial tissues in rats of each group ($\times 100$)

A: N group; B: DM4W group; C: DM8W group; D: DM8W+EtOH group

2.4 大鼠心肌PAS染色结果

与N组相比, DM4W组和DM8W组PAS阳性物质明显增多; 且DM8W组较DM4W组PAS阳性物质进一步增多; 与DM8W组相比, DM8W+EtOH组胶原纤维含量、PAS阳性物质明显减少(图3)。

2.5 大鼠心肌TASK-1的蛋白表达

与N组相比, DM4W组和DM8W组大鼠心肌TASK-1蛋白表达水平明显升高($P < 0.01$); 与DM4W组相比, DM8W组大鼠心肌TASK-1蛋白表达水平进一步升高($P < 0.01$); 与DM8W相比, DM8W+EtOH组大鼠心肌TASK-1蛋白表达水平明显降低, 但仍高于N组($P < 0.01$, 图4)。

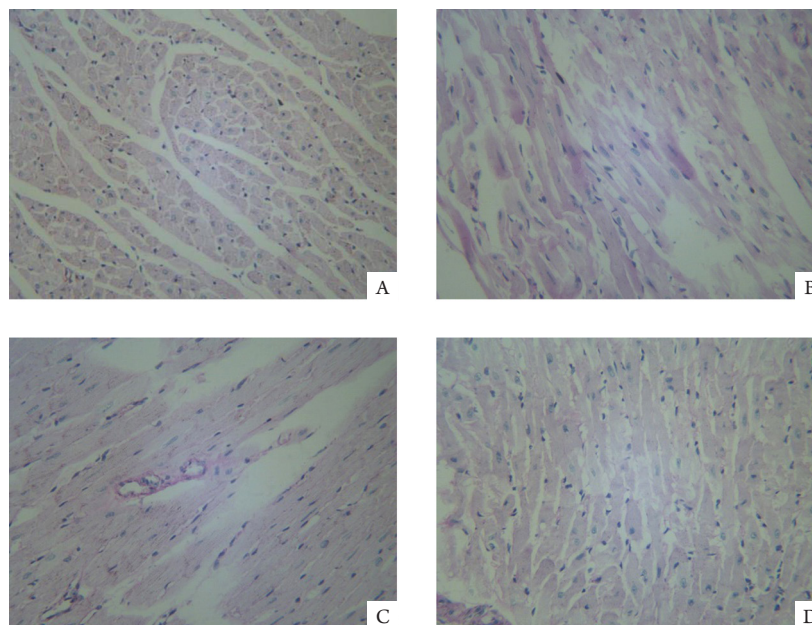


图3 各组大鼠PAS染色结果($\times 100$)

Figure 3 PAS staining of myocardial tissues in rats of each group ($\times 100$)

A: N group; B: DM4W group; C: DM8W group; D: DM8W+EtOH group

2.6 大鼠心室肌细胞TASK-1电流, APD_{30} 和 APD_{90} 的变化

钾通道具有对酸碱敏感的电生理特性, 该描记电流对酸碱敏感, 证实其为TASK-1电流。与N组相比, DM4W组和DM8W组心室肌细胞 APD_{30} 和 APD_{90} 明显延长($P<0.05$), TASK-1的电流明显减少

($P<0.01$); 且随着糖尿病病程的延长, TASK-1电流持续减少, APD_{30} 和 APD_{90} 延长明显; 与DM8W组相比, DM8W+EtOH组TASK-1电流增加明显, APD_{30} 和 APD_{90} 较前缩短(图5)。

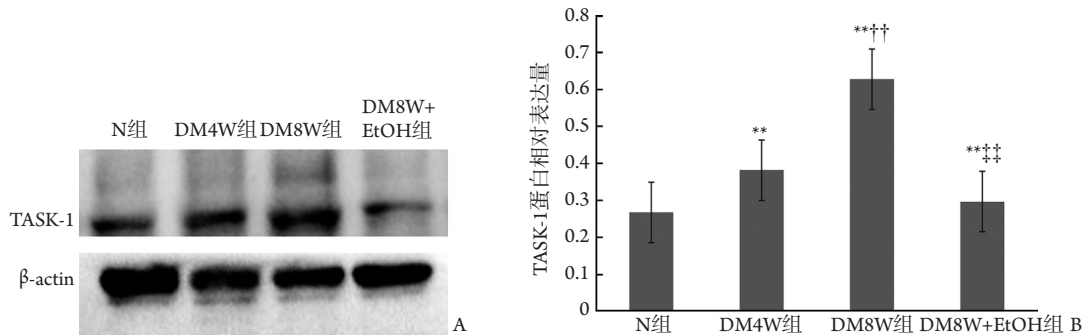


图4 Western印迹示各组大鼠心肌组织TASK-1蛋白表达水平

Figure 4 Western blot showing the TASK-1 protein expression in myocardial tissue of rats in each group

A: Electrophoregram; B: Histogram ($n=6, \bar{x}\pm s$). ** $P<0.01$ vs the N group; †† $P<0.01$ vs the DM4W group; ‡‡ $P<0.01$ vs the DM8W group

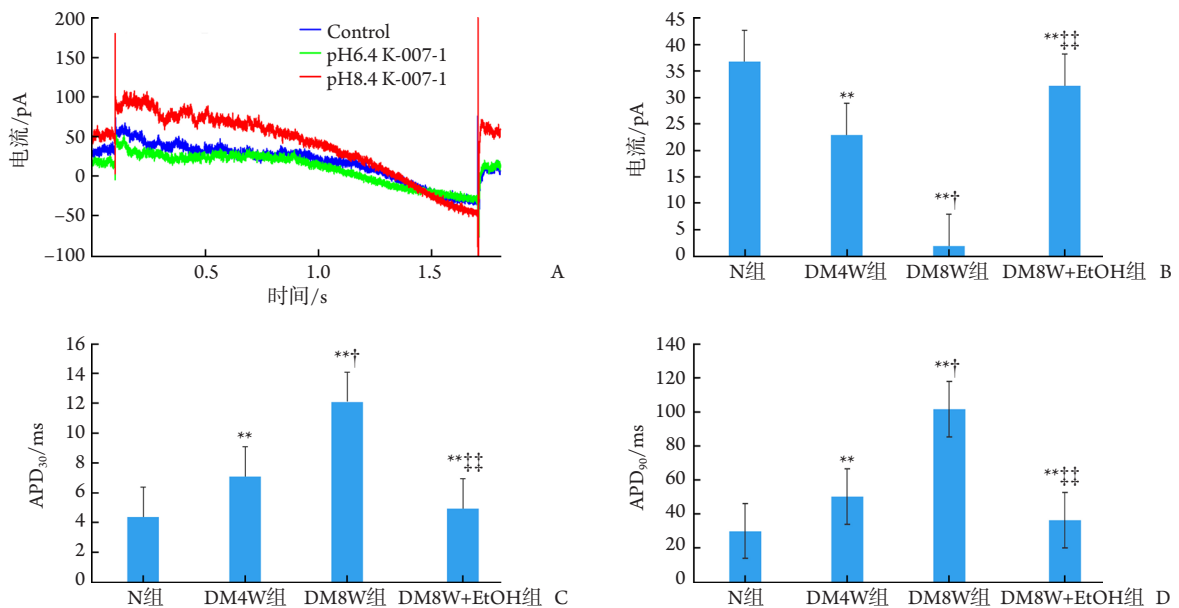


图5 各组大鼠心室肌细胞TASK-1电流, APD_{30} 和 APD_{90} 的变化($n=6, \bar{x}\pm s$)

Figure 5 Changes of TASK-1 current in ventricular myocyte and the time of ventricular myocyte APD_{30} and APD_{90} of rats in each group ($n=6, \bar{x}\pm s$)

A, B: Changes of TASK-1 current in ventricular myocyte; C, D: Time of ventricular myocyte APD_{30} and APD_{90} in different groups. ** $P<0.01$ vs the N group; † $P<0.05$ vs the DM4W group; ‡‡ $P<0.01$ vs the DM8W group

3 讨论

糖尿病对人类健康的威胁日益突出, DCM是独立于糖尿病所致的冠状动脉病变的一组特异性心肌病, 也是糖尿病患者易并发心律失常和猝死的原因。DCM具体的致病机制与心肌电生理特性之间可

能有潜在联系。本研究发现: 与N组大鼠比较, DM组大鼠心肌功能降低, 心肌细胞和纤维排列紊乱, 细胞间隙增宽, PAS染色阳性物质沉积增多, TASK-1蛋白表达增加但电流密度减少, 动作电位时程 APD_{30} 和 APD_{90} 延长明显; 与DM4W组相比, DM8W组上述改变更加明显。这提示TASK-1蛋白表达增加和电流减

少可能与糖尿病心肌损伤及心肌纤维化的进程有关。

心肌纤维化是糖尿病的并发症之一,病理学基础表现在心肌成纤维细胞过度增殖,结构紊乱,并且大量合成胶原蛋白^[16]。多种因素(炎症、缺血、缺氧等)导致细胞外基质在心肌组织中过度沉积,心肌组织中胶原浓度和胶原容积显著增加,胶原成分比例失调且排列紊乱是心肌纤维化的特征^[17-18]。心肌纤维化是心脏的一种结构重构,是对应激的一种适应性反应,也是后期引起进行性泵衰竭和/或恶性心律失常发生的根本原因。心肌中羟脯氨酸含量的变化可反映心肌总胶原含量的变化,是目前评价心肌纤维化的重要指标之一。本研究发现糖尿病导致大鼠心功能降低的同时心肌中羟脯氨酸含量增加,心肌结构出现重构,并且随着糖尿病病程的延长,大鼠心功能的降低,心肌中羟脯氨酸含量的增加和心肌结构的重构更加明显;与之前的研究^[16,18]结果一致。

心室重构包括结构重构和电重构,细胞钾离子通道在心肌细胞重构过程中起关键的作用。双孔钾离子通道是一种背景钾离子通道, TASK-1作为双孔钾离子通道家族的重要组成成员,对细胞外酸化及氧气浓度变化较为敏感,并且在心肌动作电位平台期形成、呼吸调节、肺动脉平滑肌收缩和醛固酮分泌中发挥重要作用^[19-21]。心房颤动患者心房肌组织中 TASK-1 mRNA表达水平升高;而在使用 TASK-1 阻滞剂的大鼠心室肌细胞,其动作电位明显延长,提示 TASK-1 在心肌动作电位平台期的外向电流形成中发挥作用^[22-24]。糖尿病可引起心肌细胞动作电位时程延长,而瞬时外向钾离子电流幅度降低^[25]。本课题组在前期的研究^[26]也发现:房颤大鼠 TASK-1 的蛋白表达明显增加。本实验通过应用酸碱物质检测 TASK-1 电流,发现其对酸碱较为敏感,符合 TASK-1 的电生理特性,证实该描记电流为 TASK-1 电流,同时观察到在糖尿病状态下 TASK-1 电流明显降低, TASK-1 蛋白表达明显增加,动作电位复极 30% 和 90% 的时程明显延长,且随着糖尿病病程的延长,变化更加明显。这些结果提示:糖尿病心肌细胞上双孔钾离子通道 TASK-1 受到了明显损伤, TASK-1 电流的减少和蛋白表达的增加可能是引起糖尿病心肌细胞动作电位时程延长的原因。

本研究应用 ALDH2 非特异性激动剂低浓度乙醇进一步干预,观察 ALDH2 激活后心肌组织相关指标的变化。线粒体 ALDH2 是重要的内源性心脏保护酶,与生物氧化关系密切。Fang 等^[27]研究发现: ALDH2 激活后可减少心肌细胞的坏死,从而起到保护 H9C2 心肌细胞免受高糖损伤的作用。Liu 等^[28]报道 ALDH2 激活后可通过减少有毒醛的堆积从而减轻环磷酸腺苷诱导的心脏毒性,减少心肌细胞的死亡,恢

复受损的心功能。我们前期实验也发现:长期应用低浓度乙醇可明显降低心律失常的发生,对抗离体心脏缺血再灌注损伤所致的氧化应激^[29]。在本实验中,激活 ALDH2 后,糖尿病大鼠心功能有所恢复,羟脯氨酸含量降低明显, PAS 染色阳性物质减少;这些结果提示:激活 ALDH2 后心肌损伤和纤维化的程度减轻。同时也观察到双孔钾离子通道 TASK-1 蛋白表达减少,电流密度增加明显,动作电位复极 30% 和 90% 的时程均明显缩短。这提示, ALDH2 可能通过调节双孔钾离子通道 TASK-1 蛋白和电流表达,从而减轻心肌损伤和纤维化。

综上所述,糖尿病大鼠发生心肌损伤,其心肌 TASK-1 蛋白表达上调,电流密度降低,动作电位时程延长,心肌出现纤维化,大鼠心功能受损。ALDH2 激活后,动作电位时程缩短、心肌损伤和纤维化的程度降低,同时 TASK-1 蛋白表达降低,电流密度增加。本研究首次报道在糖尿病心肌损伤后激活 ALDH2 对 TASK-1 表达的影响,推测 ALDH2 通过调节双孔钾离子通道 TASK-1 电流和蛋白的表达,起到保护心脏作用;为糖尿病在临床治疗方面提供了新思路,但关于双孔钾离子通道 TASK-1 的具体作用机制仍有待进一步探索。

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